

? b 155
 23feb99 09:28:24 User208669 Session D1383.1
 \$0.19 0.059 DialUnits File1
 \$0.19 Estimated cost File1
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 \$0.19 Estimated total session cost 0.059 DialUnits
 File 155: MEDLINE(R) 1966-1999/Apr W1
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Set Items Description

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? s py=1993:1999

S1 2337031 PY=1993:1999

? s aav or adeno(w)associated

504 AAV

1472 ADENO

615857 ASSOCIATED

680 ADENO(W)ASSOCIATED

S2 761 AAV OR ADENO(W)ASSOCIATED

? s s2 or adenoassociated

761 S2

17 ADENOASSOCIATED

S3 770 S2 OR ADENOASSOCIATED

? s specific?

S4 867589 SPECIFIC?

? s s3 and s4

770 S3

867589 S4

S5 222 S3 AND S4

? s s5 not s1

222 S5

2337031 S1

S6 73 S5 NOT S1

? t s6/7/6 8 9 14 18 24 36

6/7/6

DIALOG(R)File 155: MEDLINE(R)

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07333400 93043547

Adeno-associated virus vectors.

Carter BJ

Targeted Genetics Corporation, Seattle, Washington.

Curr Opin Biotechnol (ENGLAND) Oct 1992, 3 (5) p533-9, ISSN 0958-1669

Journal Code: A92

Languages: ENGLISH

Document type: JOURNAL ARTICLE, REVIEW, REVIEW, TUTORIAL

Adeno-associated virus is a human parvovirus that integrates its DNA genome into host cell chromosomes with very high efficiency. This suggests that adeno-associated virus may be a useful vector for human gene therapy. Interest in adeno-associated virus vectors increased greatly in the last year following reports that adeno-associated virus genome integration may be site specific and occur at preferred sites in the human genome. Several genes relevant to the treatment of genetic or infectious diseases have been expressed in adeno-associated virus vectors *in vitro*. (51 Refs.)

6/7/8

DIALOG(R)File 155: MEDLINE(R)

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07296175 92410609

Modulation of the cellular phenotype by integrated adeno-associated virus.

Winocour E; Puzis L; Etkin S; Koch T; Danovitch B; Mendelson E; Shaulian E; Karby S; Lavi S

Department of Molecular Genetics and Virology, Weizmann Institute of Science, Rehovot, Israel.

Virology (UNITED STATES) Sep 1992, 190 (1) p316-29, ISSN 0042-6822

Journal Code: XEA

Contract/Grant No.: AI-26122, AI, NIAID

Languages: ENGLISH

Document type: JOURNAL ARTICLE

The adeno-associated virus (AAV) rep gene encodes a series of overlapping, multifunctional, nonstructural proteins (Rep proteins) which regulate the viral life cycle and which are also capable of trans-regulating nonviral gene expressions (reviewed in Berns, 1990, Microbiol. Rev. 54, 316-329). To investigate the expression of the AAV rep gene in a cellular chromosomal context, SV40-transformed Chinese hamster embryo (OD4) cells were infected with an AAV/neo hybrid virus and progeny resistant to the antibiotic G418 were selected and amplified. Chromosomal integration and RNA transcription of the AAV and neo DNA inserts were confirmed by Southern and Northern blotting procedures. One of the G418R cell lines stably expressed a protein which reacted specifically with AAV anti-Rep antiserum in Western immunoblots. The stable integration of AAV rep DNA, which did not interfere with cell proliferation under normal growth conditions, was associated with two changes in cellular phenotype: eight of nine lines were markedly more sensitive to UV light (254 nm) than were the parental OD4 cells; and seven of the nine lines had lost the capacity to promote SV40 origin DNA amplification *in vitro*, in contrast to the parental OD4 cells. OD4 cells transformed to G418R by AAV/neo DNA constructs with a deleted rep gene, or by a neo DNA construct lacking AAV DNA, did not display these phenotypic changes. It is suggested that stable integration of the AAV rep gene interferes with cellular processes connected with DNA repair and gene amplification.

- 6/7/9 DIALOG(R)File 155: MEDLINE(R)
 (c) format only 1999 Dialog Corporation. All rts. reserv.
 0728855 92287906
 Gene transfer in human lymphocytes using a vector based on adeno-associated virus.
 Muro-Cacho CA; Samulski RJ; Kaplan D
 Institute of Pathology, Case Western Reserve University, Cleveland, Ohio 44106.
- J Immunother (UNITED STATES) May 1992, 11 (4) p231-7, ISSN 1053-8550
 Journal Code: AZ0
 Contract/Grant No.: AI-28923, AI, NIADDK, DK-42701, DK, NIDDK; AI-25530, AI, NIADDK
 Languages: ENGLISH
 Document type: JOURNAL ARTICLE
 Adeno-associated virus is a nonpathogenic, dependent parvovirus that integrates at a specific site in human chromosome 19. We have used the inverted terminal repeats of the virus, which mediate integration, to establish a vector for gene transfer in human lymphocytes. A neomycin resistance gene has been stably introduced into nontransformed human T-cell clones and a subsequent analysis of the functional properties of the infected clone revealed no detectable alterations. Rescue and replication of the wild-type virus was accomplished with adenovirus superinfection; however, the vector was not rescued and did not replicate by this procedure, indicating the stability of the integrated vector and demonstrating an additional level of safety incorporated in its construction. An adeno-associated virus-based vector represents an alternative to retroviruses for gene therapy in lymphocytes.

- 6/7/9 DIALOG(R)File 155: MEDLINE(R)
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 06829588 92052179
 Isolation of a candidate repressor/activator, NF-E1 (YY-1, delta), that binds to the immunoglobulin kappa 3' enhancer and the immunoglobulin heavy-chain mu E1 site.
 Park K; Atchison ML
 Department of Animal Biology, University of Pennsylvania, School of Veterinary Medicine, Philadelphia 19104.
 Proc Natl Acad Sci U S A (UNITED STATES) Nov 1 1991, 88 (21) p9804-8,
 ISSN 0027-8424 Journal Code: PV3
 Contract/Grant No.: RO1 GM42415, GM, NIGMS
 Languages: ENGLISH
 Document type: JOURNAL ARTICLE
 We have determined that the developmental control of immunoglobulin kappa 3' enhancer (kappa E3') activity is the result of the combined influence of positive- and negative-acting elements. We show that a central core in the kappa E3' enhancer is active at the pre-B-cell stage but is repressed by flanking negative-acting elements. The negative-acting sequences repress enhancer activity in a position- and orientation-independent manner at the pre-B-cell stage. We have isolated a human cDNA clone encoding a zinc finger protein (NF-E1) that binds to the negative-acting segment of the kappa E3' enhancer. This protein also binds to the immunoglobulin heavy-chain enhancer mu E1 site. NF-E1 is encoded by the same gene as the YY-1 protein, which binds to the adeno-associated virus P5 promoter. NF-E1 is also the human homologue of the mouse delta protein, which binds to ribosomal protein gene promoters. The predicted amino acid sequence of this protein contains features characteristic of transcriptional activators as well as transcriptional repressors. Cotransfection studies with this cDNA indicate that it can repress basal promoter activity. The apparent dual function of this protein is discussed.
- 6/7/14 DIALOG(R)File 155: MEDLINE(R)
 (c) format only 1999 Dialog Corporation. All rts. reserv.
 06954089 92037558
 Targeted integration of adeno-associated virus (AAV) into human chromosome 19 [published erratum appears in EMBO J 1992 Mar;11(3):1228]
 Samulski RJ; Zhu X; Xiao X; Brook JD; Housman DE; Epstein N; Hunter LA
 Department of Biological Sciences, University of Pittsburgh, PA 15260.
 EMBO J (ENGLAND) Dec 1991, 10 (12) p3941-50, ISSN 0261-4189
 Journal Code: EMB
 Contract/Grant No.: AI 25530-03, AI, NIADDK
 Languages: ENGLISH
 Document type: JOURNAL ARTICLE
 A key feature in adeno-associated virus (AAV) replication is efficient integration of the viral genome into host cell DNA to establish latency when helper virus is absent. The steps involved in this process remain largely uncharacterized, even though AAV integration was first documented 20 years ago. Using a protein-DNA binding method we isolated AAV--cellular

6/7/24

DIALOG(R)File 155:MEDLINE(R)

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06626755 90192777

Site-specific integration by adeno-associated virus.

Kotin RM; Simischko M; Samulski RJ; Zhu XD; Hunter L; Laughlin CA;

McLaughlin S; Muzychka N; Rocchi M; Berns KI

Hearst Microbiology Research Center, Department of Microbiology, Cornell University Medical College, New York, NY 10021.

Proc Natl Acad Sci U S A (UNITED STATES) Mar 1990, 87 (6) p2211-5,

ISSN 0027-8424 Journal Code: PV3

Contract/Grant No.: AI22251; AI, NIAID; GM37090, GM, NIGMS; AI25530, AI, NIAID; +

Languages: ENGLISH

Document type: JOURNAL ARTICLE

Cellular sequences flanking integrated copies of the adeno-associated virus (AAV) genome were isolated from a latently infected clonal human cell line and used to probe genomic blots derived from an additional 21 independently derived clones of human cells latently infected with AAV. In genomic blots of uninfected human cell lines and of primary human tissue, each flanking-sequence probe hybridized to unique bands, but in 15 of the 22 latently infected clones the flanking sequences hybridized not only to the original fragments but also to a total of 36 additional species. AAV probes also hybridized to 22 of these new bands, representing 11 of the 15 positive clones, but never to the fragment characteristic of uninfected cell DNA. From these data we conclude that the AAV genome preferentially integrates into a specific region of the cellular genome. We have determined that the integration site is unique to chromosome 19 by somatic cell hybrid mapping, and this sequence has been isolated from uninfected human DNA.

6/7/36

DIALOG(R)File 155:MEDLINE(R)

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06116071 87036912

Latent infection of KB cells with adeno-associated virus type 2.

Laughlin CA; Cardellchio CB; Coon HC

J Virol (UNITED STATES) Nov 1986, 60 (2) p515-24, ISSN 0022-538X

Journal Code: KCV

Contract/Grant No.: R01 AI/C1 19934, AI, NIAID

Languages: ENGLISH

Document type: JOURNAL ARTICLE

Adeno-associated virus (AAV) is a prevalent human virus whose replication requires factors provided by a coinfecting helper virus. AAV can establish latent infections in vitro by integration of the AAV genome into cellular DNA. To study the process of integration as well as the rescue of AAV replication in latently infected cells after superinfection with a helper

virus, we established a panel of independently derived latently infected cell clones. KB cells were infected with a high multiplicity of AAV in the absence of helper virus, cloned, and passaged to dilute out input AAV genomes. AAV DNA replication and protein synthesis were rescued from more than 10% of the KB cell clones after superinfection with adenovirus type 5 (Ad5) or herpes simplex virus types 1 or 2. In the absence of helper virus, there was no detectable expression of AAV-specific RNA or proteins in the latently infected cell clones. Ad5 superinfection also resulted in the production of infectious AAV in most cases. All mutant adenoviruses tested that were able to help AAV DNA replication in a coinfection were also able to rescue AAV from the latently infected cells, although one mutant, Ad5hr6, was less efficient at AAV rescue. Analysis of high-molecular-weight cellular DNA indicated that AAV sequences were integrated into the cell genome. The restriction enzyme digestion patterns of the cellular DNA were consistent with colinear integration of the AAV genome, with the viral termini present at the cell-virus junction. In addition, many of the cell lines appeared to contain head-to-tail concatemers of the AAV genome. The understanding of the integration of AAV DNA is increasingly important since AAV-based vectors have many advantages for gene transduction in vitro and in vivo.
? ds

Set	Items	Description
S1	2337031	PY=1993:1999
S2	761	AAV OR ADENO(W)ASSOCIATED
S3	770	S2 OR ADENOASSOCIATED
S4	867589	SPECIFIC?
S5	222	S3 AND S4
S6	73	S5 NOT S1 ? s promoter or promoters
S7	58468	PROMOTER
S8	14862	PROMOTERS
S9	63088	PROMOTER OR PROMOTERS ? s3 and s7 not s1
S10	770	S3 63088 S7 2337031 S1 S8 49 S3 AND S7 NOT S1 ? s8 not s6
S11	49	S8 73 S6 S9 33 S8 NOT S6 ? s9/7/4-6 8 12 16 18 21 26 31

9/7/4
DIALOG(R)File 155:MEDLINE(R)
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07382011 92348451

Chromosomal localization and organization of the murine genes encoding the beta subunits (AIC2A and AIC2B) of the interleukin 3, granulocyte/macrophage colony-stimulating factor, and interleukin 5 receptors.

Gorman DM; Itoh N; Jenkins NA; Gilbert DJ; Copeland NG; Miyajima A
Department of Molecular Biology, DNAX Research Institute of Molecular and Cellular Biology, Palo Alto, California 94304.
J Biol Chem (UNITED STATES) Aug 5 1992, 267 (22) p15842-8, ISSN 0021-9258 Journal Code: HIV
Contract/Grant No.: NO1-CO-74101, CO, NCI

Languages: ENGLISH

Document type: JOURNAL ARTICLE

Chromosomal genes for two mouse homologous beta subunits (AIC2A and AIC2B) of the interleukin-3, granulocyte/macrophage colony-stimulating factor, and interleukin-5 receptors were characterized. Both AIC2A and AIC2B genes were present on a 250-kilobase MluI restriction fragment and were mapped on murine chromosome 15 (these loci were provisionally designated as II3rb-1 (AIC2A) and II3rb-2 (AIC2B)), closely linked to the c-sis locus. Both genes consist of 14 exons and span about 28 kb each. The major transcription initiation sites of both genes were mapped at 194 bp from the initiation codon. These genes are 95% identical up to 700 bp from the transcription initiation sites. Potential recognition sequences for hemopoietic transcription factors including GATA-1 and PU.1 in addition to a TATA-like sequence are present in the 5'-flanking region. A stretch of 20 bp including the initiation site is homologous to the corresponding region of the erythropoietin receptor and the interleukin-7 receptor genes and to the initiator sequence of the adeno-associated virus P5 promoter, suggesting a possible role in transcription initiation. Comparison of the exon/intron boundaries of AIC2A and AIC2B genes with those of other members of the cytokine receptor superfamily reveals a conserved evolutionary structure. Isolation of various forms of AIC2 cDNAs reveals differential splicing of the transcripts.

9/7/5

DIALOG(R)File 155: MEDLINE(R)

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07330679 90329218

The recombinant human parvoviruses for gene therapy of hemoglobinopathies.

Dixit M; Tillary MK; Plonk SG; Ohi S

Department of Biochemistry, Meharry Medical College, Nashville, TN 37208.
SAAS Bull Biochem Biotechnol (UNITED STATES) Jan 1990, 3 p63-8,
Journal Code: ALK
Contract/Grant No.: HL01989, HL, NHLBI; HL38737, HL, NHLBI

Languages: ENGLISH

Document type: JOURNAL ARTICLE

Towards a goal of using adeno-associated viruses (AAV), the human parvovirus, as the gene transfer vector for gene therapy of hemoglobinopathies, the human beta-globin (*h* beta *G*) cDNA was ligated downstream of the P40 promoter of AAV type 2 (AAV2) genome. Transfection via electroporation of the construct into human 293 cells (embryonal kidney cell line) resulted in expression of the cloned *h* beta *G* cDNA, as evidenced by the synthesis of transcripts hybridizable to *h* beta *G* probe. The transfection led to the recombinant genome to be excised out of the plasmid and replicate in the cell, followed by production of the recombinant AAV that harbors *h* beta *G* cDNA.

9/7/6

DIALOG(R)File 155: MEDLINE(R)

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07302580 93099882

Characterization of a preferred site on human chromosome 19q for integration of adeno-associated virus DNA by non-homologous recombination. Kotin RM; Linden RM; Berns KI
Molecular Hematology Branch, National Institutes of Health, Bethesda, MD 20892.

EMBO J (ENGLAND) Dec 1992, 11 (13) p5071-8, ISSN 0261-4189

Journal Code: EMB

Contract/Grant No.: AI 222251, AI, NIAID

Languages: ENGLISH

Document type: JOURNAL ARTICLE

The human parvovirus, adeno-associated virus (AAV), has been shown to integrate preferentially into human chromosome 19 q13.3-qter. The human target sequence for AAV integration (AAVS1) was cloned and sequenced. By analysis of the proviral junctions it was determined that integration of the AAV DNA occurred via a non-homologous recombination pathway although there were either four or five identical nucleotides at the junctions. Integration was a multistep, concerted process that resulted in cellular sequence rearrangements. The sequence of the integration locus was analyzed for possible recombination signals. Direct repeats at a much greater than random occurrence were found distributed non-uniformly throughout the AAVS1 sequence. A CpG island containing transcription factor binding site elements is suggestive of a TATA-less promoter. Evidence for transcriptional activity was provided by PCR amplification of reverse transcribed RNA.

9/7/8

DIALOG(R)File 155: MEDLINE(R)

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07295326 92392571

Gene expression from adeno-associated virus vectors in airway epithelial cells.

Flotte TR; Solow R; Owens RA; Afione S; Zeitlin PL; Carter BJ

Laboratory of Molecular and Cellular Biology, National Institute of Diabetes, Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD 20892.

Am J Respir Cell Mol Biol (UNITED STATES) Sep 1992, 7 (3) p349-56,
ISSN 1044-1549 Journal Code: AOB

Languages: ENGLISH

Document type: JOURNAL ARTICLE

Lung diseases such as cystic fibrosis (CF) might be treated by gene therapy using viral vectors delivered to the airway. One potential vector is the defective human parvovirus, adeno-associated virus (AAV). We examined the AAV p5 transcription promoter for gene expression in immortalized cell lines derived from the airway (IB3-1) or pancreas (CFPAC-1) of CF patients. AAV vectors expressing the prokaryotic genes cat (pAAVp5cat) or neo (pAAVp5neo) from the p5 promoter were evaluated after introduction into IB3-1 or CFPAC-1 cells by lipofection. In transient assays in both cell lines, the cat gene was expressed 5- to 10-fold more efficiently from the p5 promoter than from a simian virus 40 early gene promoter (pSVcat). IB3-1 cells were transformed stably to geneticin resistance by pAAVp5neo at a 5-fold higher efficiency than by an SVneo vector. The AAV inverted terminal repeat (ITR) region immediately upstream of the p5 promoter appears to have an enhancer effect and the promoter also contains a CREB site which confers a response to forskolin. In IB3-1 cells, expression of the cat gene from a p5 promoter was decreased about 5-fold by deletion of both the upstream ITR and the CREB site. The AAVp5neo vector was also packaged into AAV particles and used to infect IB3-1 cells as a transducing virus. Under these conditions, 60 to 70% of the cells could be stably transformed to geneticin resistance. Thus, AAV transducing vectors appear to be a highly efficient delivery system for stable integration and expression of genes in cultured airway epithelial cells.

9/7/12
DIALOG(R)File 155:MEDLINE(R)
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06952402 92009221

Construction and expression of a recombinant adeno-associated virus that harbors a human beta-globin-encoding cDNA.
Dixit M; Webb MS; Smart WC; Ohi S
Department of Biochemistry, School of Medicine, Meharry Medical College, Nashville, TN.

Gene (NETHERLANDS) Aug 15 1991, 104 (2) p253-7, ISSN 0378-1119
Journal Code: FOP
Contract/Grant No.: HL019898, HL, NHLBI; HL38737, HL, NHLBI
Languages: ENGLISH

Document type: JOURNAL ARTICLE

Towards a goal of using recombinant adeno-associated viruses (AAV) for the gene therapy of hemoglobinopathies we had previously constructed plasmid pAV h beta G psi 1, which contained a human beta-globin-encoding

cDNA (HB2) downstream from the P40 promoter of AAV2 DNA [Ohi et al., Gene 89 (1990) 279-282]. Transfection of the plasmid into human 293 cells (embryonal kidney cell line) resulted in the expression of HB2 at the mRNA level as well as rescue and replication of the recombinant AAV genome (Ohi et al., ibid.). The present study demonstrates that the replicated recombinant DNA was packaged into an intact virion by transcomplementation with pAV2 or the defective helpers, pAV delta Bam or pAVXB. The recombinant virus could be isolated by equilibrium CsCl density gradient, the density of which was about 1.4 g/cm3. The defective helpers are used to produce wild-type AAV-free recombinant AAV. The recombinant AAV were infectious and expressed chimeric mRNAs containing the HB2 sequence in virus-infected 293, KB (oral epidermoid carcinoma cell line) and K562 (human erythroleukemia cell line) cells. The importance of the infectivity and expression of the recombinant AAV in hematopoietic cells is discussed in the context of gene therapy of hemoglobinopathies.

9/7/16
DIALOG(R)File 155:MEDLINE(R)
(c) format only 1999 Dialog Corporation. All rts. reserv.
0634298 90323629
Construction and replication of an adeno-associated virus expression vector that contains human beta-globin cDNA.
Ohi S; Dixit M; Tillery MK; Plonk SG
Department of Biochemistry, School of Medicine, Meharry Medical College, Nashville, TN 37208.

Gene (NETHERLANDS) May 14 1990, 89 (2) p279-82, ISSN 0378-1119
Journal Code: FOP
Contract/Grant No.: HL01989, HL, NHLBI; HL38737, HL, NHLBI
Languages: ENGLISH
Document type: JOURNAL ARTICLE

With the goal of using adeno-associated viruses (AAV) as the gene-transfer vector for gene therapy of hemoglobinopathies, human beta-globin cDNA was ligated downstream from the P40 promoter of the AAV type-2 (AAV2) genome. To circumvent difficulties of cloning DNA containing palindromic sequences, two of which exist in the termini of AAV genome, a step-wise approach handling one palindrome at a time was devised to construct the chimeric expression vector. Electroporation of the construct into human 293 cells (embryonal kidney cell line) resulted in expression of the cloned human beta-globin cDNA, as evidenced by the synthesis of transcripts hybridizable to human beta-globin cDNA probe. Addition of the 3'-end region of AAV DNA that contains both the transcription termination signal and origin of DNA replication for AAV to the construct permitted the recombinant AAV genome to be rescued and replicate in the cell.

9/7/18
DIALOG(R)File 155:MEDLINE(R)
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06306491 88322865

Expression and rescue of a nonselected marker from an integrated AAV vector.

Mendelson E; Smith MG; Carter BJ

Laboratory of Molecular and Cellular Biology, National Institute of Diabetes, Digestive, and Kidney Diseases, Bethesda, Maryland 20892.

Virology (UNITED STATES) Sep 1988, 166 (1) p154-65, ISSN 0042-6822

Journal Code: XEA

Languages: ENGLISH

Document type: JOURNAL ARTICLE

We used rep+ and rep- recombinant AAV-plasmid vectors containing the nonselectable marker chloramphenicol acetyltransferase (CAT) driven by the AAV p40 promoter, and having a selectable marker, neo, inserted in the plasmid genome, and driven by a herpesvirus thymidine kinase gene promoter. Each vector was transfected into human 293 cells or HeLa cells and the neo gene was used to select geneticin-resistant (genr) cells containing integrated vectors. The genr cells were then screened for expression of the unselected marker CAT. For 293 cells, most clones from the rep- vector gave high CAT expression whereas only 50% of those from the rep+ vector expressed CAT, generally at low level. For HeLa cells about 25% of the clones derived from either the rep+ or rep- vector expressed CAT, and several clones from the rep+ vector gave very high yields. We also analyzed integrated rep+ vectors by rescue after superinfection with adenovirus and by Southern blotting. The AAV-CAT genome could be rescued from 50% of HeLa cell clones but not from 293 cell clones. Lack of rescueability reflected rearrangement of the AAV genome termini or the rep gene. Western blotting showed low level constitutive expression of rep protein in one 293 cell clone and two HeLa cell clones. Thus, the AAV p40 promoter (as well as p5 and p19) can function in integrated vectors to express unselected markers which can subsequently be rescued. Expression and rescue depended upon several parameters including the cell type, the initial structure of the vector (rep+ or rep-) but not continued expression of rep, and possibly global effects of the surrounding chromatin.

9/7/21 DIALOG(R)File 155: MEDLINE(R)

(C) format only 1999 Dialog Corporation. All rts. reserv.

06265856 86310795

Adeno-associated virus vector for high-frequency integration, expression, and rescue of genes in mammalian cells.

Tratschin JD; Miller L; Smith MG; Carter BJ

Mol Cell Biol (UNITED STATES) Nov 1985, 5 (11) p3251-60, ISSN 0270-7306 Journal Code: NGY

Languages: ENGLISH

Document type: JOURNAL ARTICLE

We describe the construction of an adeno-associated virus (AAV) vector in which the coding sequence of the procaryotic gene neo is expressed under

the control of the major AAV promoter p40. This AAV-neo vector allowed stable expression of neo as a dominant selective marker in mammalian cells by selection of cells which were resistant to the antibiotic geneticin (G418). When the vector was introduced into human (293 or HeLa) cell lines by a DNA transfection procedure, stable geneticin-resistant colonies were obtained. When the vector was first packaged into AAV particles and then introduced into cells via particle infection, geneticin-resistant cells were obtained at higher frequencies than those obtained by DNA transfection. In geneticin-resistant cells the AAV-neo vector was integrated at low copy number and could be rescued by subsequent infection with wild-type AAV and the helper adenovirus or, in some cases, by infection with adenovirus alone. The rescued AAV-neo vector could then be recovered as amplified unintegrated DNA from a Hirt lysate. These results demonstrate that AAV can be used as a transducing viral vector for stable integration and expression of a foreign gene in mammalian cells. The high frequency of integration and the ability to rescue the integrated vector suggest that this vector system may be useful for selecting genes from cDNA libraries. This vector may also be useful for introduction of genes into cells which are refractory to transfection in procedures such as those involving the use of CaPO4 or DEAE-dextran.

9/7/26

DIALOG(R)File 155: MEDLINE(R)

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06133420 87321122

Gene expression in adeno-associated virus vectors: the effects of chimeric mRNA structure, helper virus, and adenovirus VAI RNA.

West MH; Trempe JP; Tratschin JD; Carter BJ

Virology (UNITED STATES) Sep 1987, 160 (1) p38-47, ISSN 0042-6822

Journal Code: XEA

Languages: ENGLISH

Document type: JOURNAL ARTICLE

We used a recombinant plasmid containing an adeno-associated virus (AAV) genome to construct several vectors which express the gene for chloramphenicol acetyltransferase (CAT). We transfected four different AAV-CAT vectors into human 293 (adenovirus-transformed) cells and analyzed CAT activity. We show that, for vectors using the AAV p40 and p19 promoter, the chimeric AAV-CAT transcripts began from the correct 5' position but the basal level of CAT expression depended in part on the structure of the transcript. We also examined the effects of coinfection of the cells with the helper adenovirus or cotransfection with a plasmid which expressed the adenovirus translational control RNA, VAI RNA. Cotransfection with plasmids containing the gene for VAI RNA resulted in elevated levels of CAT activity. VAI RNA stimulated translation of the chimeric mRNA. However, in two cases, the VAI RNA apparently decreased the level of mRNA. These results suggest that in addition to its function in translation, VAI RNA acts at a second site to alter cytoplasmic accumulation of some mRNAs.

Infection with adenovirus increased CAT activity several-fold by increasing the cytoplasmic levels of the chimeric AAV-CAT transcript. When the CAT gene is inserted down stream of the AAV inton, adenovirus and not VA1 RNA alone increased CAT activity by promoting accumulation of a spliced transcript.

? ds

Set Items Description
 S1 2337031 PY=1993:1999
 S2 761 AAV OR ADENO(W)ASSOCIATED
 S3 770 S2 OR ADENOASSOCIATED
 S4 867589 SPECIFIC?

9/7/31 DIALOG(R)File 155:MEDLINE(R)

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05368677 88288213

Cloning of the human thyrotropin beta-subunit gene and transient expression of biologically active human thyrotropin after gene transfection.

Wondisford FE; Usala SJ; DeCherney GS; Castren M; Radovick S; Gyves PW; Trempe JP; Kerfoot BP; Nikodem VM; Carter BJ; et al
 Molecular, Cellular and Nutritional Endocrinology Branch, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, Maryland 20892.

Mol Endocrinol (UNITED STATES) Jan 1988, 2 (1) p32-9, ISSN 0888-8809

Journal Code: NGZ

Languages: ENGLISH

Document type: JOURNAL ARTICLE

A 17 kilobase pair fragment of DNA containing the human TSH (hTSH) beta-subunit gene was isolated from a human leukocyte genomic library. Using a 621 base pair human CG alpha-subunit cDNA and a 2.0 kilobase pair genomic fragment of hTSH beta containing both coding exons, we constructed hCG alpha and hTSH beta expression vectors containing either the early promoter of simian virus 40 or the promoters of adeno-associated virus.

Cotransfection of two adeno-associated virus vectors, each containing one subunit of hTSH, together with a plasmid containing the adenovirus VA RNA genes produced hTSH as well as free human alpha- and TSH beta-subunits in an adenovirus transformed human embryonal kidney cell line (293). The levels of protein expression in this system were 10- to 100-fold greater than that found in a simian virus transformed monkey kidney cell line (COS) using vectors containing the early promoter of simian virus 40. The hTSH synthesized in 293 cells was glycosylated as indicated by complete binding to concanavalin A-Sepharose but was larger in apparent molecular weight than a standard hTSH preparation on gel chromatography suggesting an altered glycosylation pattern. However, it was immunologically and biologically indistinguishable from two pituitary hTSH standards in an immunoradiometric and in vitro iodide trapping assay, respectively.

? expression(1a)control?

S10 0 EXPRESSION(1A)CONTROL?

? express?(2n)control?

463257 EXPRESS?

1188330 CONTROL?

S11 7846 EXPRESS?(2N)CONTROL?

Set Items Description
 S1 2337031 PY=1993:1999
 S2 73 S5 NOT S1
 S7 63088 PROMOTER OR PROMOTERS
 S8 49 S3 AND S7 NOT S1
 S9 33 S8 NOT S6
 S10 0 EXPRESSION(1A)CONTROL?
 S11 7846 EXPRESS?(2N)CONTROL?
 ? s11 and s2 not (s1 or s6 or s9)
 7846 S11
 761 S2
 2337031 S1
 73 S6
 33 S9
 S12 0 S11 AND S2 NOT (S1 OR S6 OR S9)

? save temp
 Temp SearchSave "TD511" stored
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 >>>No valid files specified
 ? b 350
 >>> 350 does not exist
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 23feb99 09:43:38 User208669 Session D1383.2
 \$7.91 2.635 DialUnits File155
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 \$3.40 17 Type(s) in Format 7
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 \$11.31 Estimated cost File155
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 \$11.31 Estimated cost this search
 \$11.50 Estimated total session cost 2.695 DialUnits

File 357:Derwent Biotechnology Abs 1982-1999/Feb B2

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Set Items Description
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restrict both HIV virus-1 and SIV replication. Both HIV virus-1 and SIV production were inhibited in the antisense clones, SIV to a lesser degree than HIV virus-1. There was 85% inhibition of SIV replication in clone IIC4 and 92% inhibition of HIV on day 3 posttransfection. (69 ref)

- Set Items Description
 S1 84703 PY=1993:1999
 S2 504 AAV OR ADENO(W)ASSOCIATED
 S3 504 S2 OR ADENOASSOCIATED
 S4 44778 SPECIFIC?
 S5 140 S3 AND S4
 S6 5 S5 NOT S1
 S7 17783 PROMOTER OR PROMOTERS
 S8 16 S3 AND S7 NOT S1
 S9 16 S8 NOT S6
 S10 0 EXPRESSION(1A)CONTROL?
 S11 2028 EXPRESS?(2N)CONTROL?
 S12 0 S11 AND S2 NOT (S1 OR S6 OR S9)
 ?ts67/1 2 3 5
- LANGUAGE: English
ABSTRACT: Recombinant adeno-associated virus-2 (AAV2) vectors harboring human beta-globin (hbG) cDNA were constructed. Chimeric plasmid pAVhbG-psl-1 was constructed as previously described. Plasmid pAV-delta-KhbG was constructed by inserting a full-length hbG cDNA into pAV2-delta-K. The recombinant virus was produced by transfecting the chimeric plasmid into 293 cells together with plasmid pAV2 and AA V2, and preparing the cell lysate at 48 hr post-infection. Upon transfection into 293 cells, the recombinant AA V2 DNA harboring hbG cDNA was rescued from the plasmid and replicated in the cells. This in turn resulted in the production of infectious recombinant AAV. AVhbG-psl-1 expressed mRNA in the virus-infected 293, KB and K562 cells. The second recombinant virus, A V-delta-KhbG expressed hbG protein in the infected 293 cells. To make the expression of hbG cDNA/gene specific to erythroid cells, the erythroid-specific 5'-enhancer elements, DCR/LAR, were spliced into the genome of the recombinant virus. (3 ref)
- 6/7/1
 DIALOG(R)File 357:Derwent Biotechnology Abs
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 0144085 DBA Accession No.: 93-02137
 Status of ribozyme and antisense-based developmental approaches for anti-HIV-1 therapy - adeno-associated virus vector for antisense DNA and antisense RNA expression for HIV virus-1 gene therapy (conference paper)
 AUTHOR: Zaia J A; Chatterjee S; Wong K K; Elkins D; Taylor N R; Rossi J J
 CORPORATE SOURCE: Division of Pediatrics, City of Hope National Medical Center, Duarte, California 91010-0269, USA.
 JOURNAL: Ann.N.Y.Acad.Sci. (660, 95-106) 1992
 CODEN: ANYAA9
 LANGUAGE: English
ABSTRACT: The adeno-associated virus (AAV) may be a candidate vector for use in viricide gene therapy. Antisense DNA and RNA have been shown to inhibit HIV virus-1 as either synthetic DNA or expressed RNA (intracellular immunization). Systems are being developed for inserting into the host cell genome the DNA sequences that could potentially confer resistance to HIV virus replication. A modified vector system based on the nonpathogenic, replication-defective parvo virus AAV. AAV directs the stable integration of foreign DNA encoding an HIV virus-1-specific antisense RNA. The target for the antisense RNA-transcript is the TAR sequence (a cis-acting RNA stem-loop structure in the HIV virus-1 long terminal repeat). The targeted region, TAR, is highly conserved between HIV virus-1 and SIV virus. Antisense-expressing clonal cell lines were tested for their ability to
- 6/7/2
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 0138156 DBA Accession No.: 92-10648
 Development of recombinant adeno-associated viruses that harbor human beta-globin cDNA/gene towards gene therapy of hemoglobinopathies - adeno-associated virus vector plasmid pAV-delta-KhbG construction and expression in 293, KB and K562 cell culture (conference abstract)
 AUTHOR: Ohi S; Webb M S; Sitaric S
 CORPORATE SOURCE: Department of Biochemistry, Meharry Medical College, Nashville, TN 37208, USA.
 JOURNAL: Miami Short Rep. (1, 116) 1991
 CODEN: 9999Y
- LANGUAGE: English
ABSTRACT: Recombinant adeno-associated virus-2 (AAV2) vectors harboring human beta-globin (hbG) cDNA were constructed. Chimeric plasmid pAVhbG-psl-1 was constructed as previously described. Plasmid pAV-delta-KhbG was constructed by inserting a full-length hbG cDNA into pAV2-delta-K. The recombinant virus was produced by transfecting the chimeric plasmid into 293 cells together with plasmid pAV2 and AA V2, and preparing the cell lysate at 48 hr post-infection. Upon transfection into 293 cells, the recombinant AA V2 DNA harboring hbG cDNA was rescued from the plasmid and replicated in the cells. This in turn resulted in the production of infectious recombinant AAV. AVhbG-psl-1 expressed mRNA in the virus-infected 293, KB and K562 cells. The second recombinant virus, A V-delta-KhbG expressed hbG protein in the infected 293 cells. To make the expression of hbG cDNA/gene specific to erythroid cells, the erythroid-specific 5'-enhancer elements, DCR/LAR, were spliced into the genome of the recombinant virus. (3 ref)
- 6/7/3
 DIALOG(R)File 357:Derwent Biotechnology Abs
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 0134768 DBA Accession No.: 92-07260
 Gene transfer in human lymphocytes using a vector based on adeno-associated virus - B-lymphocyte, T-lymphocyte transformation using AA V/neeo vector, which may be useful in gene therapy
 AUTHOR: Muro-Cacho C A; Samulski R J; +Kaplan D
 CORPORATE SOURCE: Institute of Pathology, Case Western Reserve University, 2085 Adelbert Road, Cleveland, OH 44106, USA.
 JOURNAL: J.Immunother. (11, 4, 231-37) 1992

CODEN: 5592H

LANGUAGE: English

ABSTRACT: The inverted terminal repeats of adeno-associated virus (AAV), which mediate integration at a specific site in human chromosome-19, were used to establish a vector for gene transfer into human lymphocytes. Epstein-Barr virus-transformed B-lymphocyte JY cells were infected with vector AAV/heo containing the neomycin-resistance gene and AAV inverted terminal repeats in place of the AAV coding region. A neomycin-resistant cell was isolated after 4 wk in the presence of G418. Non-transformed T-lymphocyte CAN.1 was infected with AAV/heo during cloning. While uninfected CAJO-10 cells (control) showed a marked reduction in proliferative activity in the presence of G418, transformed CAN.1 was not affected. There were no detectable alterations in the functional properties of CAN.1. Rescue and replication of wild-type AAV occurred with AAV super-infection. However, the vector was not rescued and did not replicate, indicating the stability of the integrated vector and demonstrating an additional level of safety incorporated in its construction. An AAV vector may be a viable alternative to retro viruses for gene therapy in lymphocytes. (32 ref)

6/7/5

DIALOG(R)File 357:Derwent Biotechnology Abs

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0086365 DBA Accession No.: 89-04356 PATENT

Stable and viable recombinant animal cell virus vector construction - by contacting Cre with a virus vector containing a lox site and circular DNA containing a lox site
PATENT ASSIGNEE: Du-Pont 1989

PATENT NUMBER: EP 300422 PATENT DATE: 890125 WPI ACCESSION NO.: 89-025608
(8904)

PRIORITY APPLIC. NO.: US 77145 APPLIC. DATE: 870721

NATIONAL APPLIC. NO.: EP 88111596 APPLIC. DATE: 880719

LANGUAGE: English

ABSTRACT: A method for preparing a stable and viable recombinant virus vector for animal cells by site-specific insertion of a DNA fragment into a virus vector comprises: (1) contacting Cre with a 1st lox site, which has been introduced into the DNA of the animal cell virus vector, and (2) contacting Cre with a 2nd lox site in a separate DNA molecule, which is circular so that Cre effects recombination of the circular DNA with the virus vector DNA at the 1st lox site. The initial virus vector preferably contains a selectable marker gene. The DNA fragment preferably lacks the selectable marker. The 1st lox site is introduced into a nonessential region of the vector, e.g. the gIII gene of pseudorabies virus. The DNA fragment preferably encodes a structural protein, an enzyme, a regulatory molecule, or a fragment of any of

these. Each of the lox sites is preferably a loxP or a loxC2 site and the vector is preferably SV40, pseudorabies virus, polyoma virus, an adeno virus, an adeno-associated virus, herpes virus, vaccinia virus, cattle papilloma virus, Epstein-Barr virus, a baculo virus or a retro virus, especially RPV42. (19pp)
? ds

Set	Items	Description
S1	84703	PY=1993:1999
S2	504	AAV OR ADENO(W)ASSOCIATED
S3	504	S2 OR ADENOASSOCIATED
S4	44778	SPECIFIC?
S5	140	S3 AND S4
S6	5	S5 NOT S1
S7	17783	PROMOTER OR PROMOTERS
S8	16	S3 AND S7 NOT S1
S9	16	S8 NOT S6
S10	0	EXPRESSION(1A)CONTROL?
S11	2028	EXPRESS?(2ND)CONTROL?
S12	0	S11 AND S2 NOT (S1 OR S6 OR S9) ? ts9/7/1 3-7 9 10

9/7/1

DIALOG(R)File 357:Derwent Biotechnology Abs

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0140400 DBA Accession No.: 92-12892 PATENT

New adeno-associated virus-2 hybrid gene vector - for foreign gene integration and DNA rescue in mammal cell culture using a helper virus,
e.g. plasmid ins 96/lambdAM

PATENT ASSIGNEE: Univ.Florida-Res.Found. 1992
PATENT NUMBER: US 5139941 PATENT DATE: 920818 WPI ACCESSION NO.: 92-299352 (9236)

PRIORITY APPLIC. NO.: US 785224 APPLIC. DATE: 911025

NATIONAL APPLIC. NO.: US 785224 APPLIC. DATE: 911025

LANGUAGE: English

ABSTRACT: A new hybrid gene vector (capable of transduction of foreign DNA into a mammal cell in the presence of a promoter other than an adeno-associated virus (AAV) transcription promoter) comprises foreign DNA ligated into an AAV-2 genome, in place of or in addition to the cap, lip or rep coding sequence or an AAV sequence excluding the 1st and last 145 bp. The AAV genome is cloned in a prokaryotic or yeast plasmid or phage vector (e.g. plasmid pBR322), and may be the entire AAV DNA or a deletion mutant (e.g. d152-91 or d13-94), capable of replication on infection of the mammal cell when complemented in trans by an AAV gene. Methods of transducing foreign DNA into mammal cells by infection of cells with the vector, and methods of rescuing foreign DNA from transduced cells by infection with a helper virus (e.g. plasmid

ins 96/lambda-M) containing genes for replication of the AAV genome or production of AAV, are also new. The vector may be used for reliable insertion of foreign DNA into mammal cells, so that the transferred genetic material is stable with respect to the insertion locus, and which is susceptible to expression and rescue. (12pp)

9/7/3

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0128750 DBA Accession No.: 92-01242

Construction and expression of a recombinant adeno-associated virus that harbors a human beta-globin-encoding cDNA - potential use in gene therapy of thalassemia or sickle cell anemia; gene cloning in KB, K562 and 293 cell culture; vector construction

AUTHOR: Dixit M, Webb M S, Smart W C, +Ohi S

CORPORATE SOURCE: Department of Biochemistry, Meharry Medical College, 1005 D.B. Todd Jr. Blvd., Nashville, TN 37208, USA.

JOURNAL: Gene (104, 2, 253-57) 1991

CODEN: GENED6

LANGUAGE: English

ABSTRACT: With the goal of using recombinant adeno-associated virus (AAV) for gene therapy of hemoglobinopathies, plasmid pAVh-beta-G-psi-1 was constructed previously, with a human beta-globin cDNA (HBB) gene downstream from the P40 promoter of AAV-2 DNA. Transfection of a 293 cell culture with the plasmid resulted in expression of HBB at the mRNA level, and rescue and replication of the recombinant AAV genome. The replicated recombinant DNA was packaged into an intact virion by trans-complementation with plasmid pAV2 or defective helper plasmids (plasmid pAV-delta-Bam or plasmid pAVXB). The recombinant virus could be isolated by equilibrium cesium chloride density gradient centrifugation, at a density of 1.4 g/cm³. The defective helpers were used to produce wild-type AAV-free recombinant AAV. The recombinant AAV was infectious, and produced chimeric mRNA containing the HBB sequence in virus-infected 293, KB (oral epidermoid carcinoma) and K562 (human erythroleukemia) cells. These results may be useful in designing strategies for gene therapy of thalassemia or sickle cell anemia. (29 ref)

PATENT NUMBER: US 7527195 PATENT DATE: 910702 WPI ACCESSION NO.: 91-237708 (9132)
 PRIORITY APPLIC. NO.: US 527195 APPLIC. DATE: 900523
 NATIONAL APPLIC. NO.: US 527195 APPLIC. DATE: 900523
 LANGUAGE: English

ABSTRACT: Adeno-associated virus (AAV)-based eukaryotic vectors, and cells transfected with these vectors, are new. The vectors are free of AAV coding sequences and consist of: (a) endogenous cis-active DNA for AAV DNA replication, encapsidation and host cell replication; (b) a heterologous DNA fragment, operably linked to (b) and (c) and present in the sense or antisense direction. The heterologous DNA fragment can encode a foreign protein or viral component. Specified AAV-based eukaryotic vectors (e.g. CWRSV:HIV-ASN and CWRSV:SSN) confer intracellular resistance to HIV virus-1 and herpes simplex virus-1 (HSV-1) infection. The vectors can be used to down-regulate a targeted viral (HIV-1, HSV-1) or cellular (histocompatibility gene involved in graft rejection) gene of known sequence, or for protein expression. In a preferred process, the AAV-based vectors are used to produce an antisense mRNA complementary to a 5'-noncoding region of the primary HIV-1 RNA transcript including the core TAR sequence. The mRNA inhibits HIV-1 replication and infectious particle production. (69pp)

9/7/5

DIALOG(R)File 357:Derwent Biotechnology Abs

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0110288 DBA Accession No.: 90-12979

Construction of recombinant adeno-associated virus that harbors human beta-globin cDNA - vector construction for potential application in hemoglobinopathy gene therapy; gene cloning and expression in 293 cell culture (conference abstract)

AUTHOR: Ohi S, Dixit M, Tillary M K, Plonk S G

CORPORATE SOURCE: Department of Biochemistry, Meharry Medical College, Nashville, TN 37208, USA.

JOURNAL: J Cell Biochem. (Suppl.14A, D422) 1990

CODEN: JCBD5

LANGUAGE: English

ABSTRACT: The possibility of developing human recombinant parvo virus vectors containing normal alpha-globin or beta-globin cDNA genes for gene therapy of hemoglobinopathies was investigated. The human beta-globin cDNA was excised from JW102 using S1 -nuclease and ligated with adeno-associated virus-2 (AAV2) DNA in plasmid pAV2, downstream of the P40 promoter. Cloning of this construct in Escherichia coli DH5 resulted in isolation of recombinant plasmid pAVHbetaGHP11. Transfection via electroporation into human 293 cell culture resulted in expression of the beta-globin cDNA, as evidenced by biosynthesis of transcripts hybridizing to a human beta-globin cDNA probe. Addition of

9/7/4

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0124445 DBA Accession No.: 91-12087 PATENT

New adeno-associated virus-derived eukaryotic vector - containing heterologous DNA for protein expression or especially down-regulation of target e.g. HIV virus-1 or herpes simplex virus-1 gene; intracellular immunization and gene therapy

PATENT ASSIGNEE: Nat.Inst.Health-Bethesda 1991

the 3'-end region of AAV DNA containing both a transcription termination signal and the replication origin for AAV to plasmid pAVHbetaGHP11 resulted in production of plasmid pAVHbetaGpsi1. Transfection of this construct into 293 cells permitted the recombinant AAV DNA containing the beta-globin cDNA to replicate inside the cell. This, in turn, resulted in production of the infectious recombinant virus. (0 ref)

9/7/6

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0110266 DBA Accession No.: 90-12957

Construction and replication of an adeno-associated virus expression vector that contains human beta-globin cDNA - plasmid pAVh-beta-GHP11 and plasmid pAVh-beta-G-psi1 construction; potential application in gene therapy of e.g. sickle cell anemia or thalassemia

AUTHOR: Ohi S; Dixit M; Tillery M K; Plonk S G

CORPORATE SOURCE: Department of Biochemistry, Meharry Medical College, 1005

D.B. Todd Jr. Blvd., Nashville, TN 37208, USA.

JOURNAL: Gene (89, 2, 279-82) 1990

CODEN: GENED6

LANGUAGE: English

ABSTRACT: With the goal of using an adeno-associated virus (AAV) as a gene transfer vector for gene therapy of hemoglobinopathies (e.g. sickle cell anemia or thalassemia), human beta-globin cDNA was ligated downstream from the P40 promoter of the AAV-2 genome. To circumvent difficulties of cloning DNA containing palindromic sequences, 2 of which exist in the termini of the AAV genome, a stepwise approach handling 1 palindrome at a time was devised to construct a chimeric expression vector, plasmid pAVh-beta-GHP11. Electroporation of the construct into a human 293 cell culture resulted in expression of the cloned human beta-globin cDNA, as evidenced by the biosynthesis of transcripts hybridizable to a human beta-globin cDNA probe. Addition of the 3'-end region of AAV DNA containing both the transcription termination signal and DNA replication origin for AAV to the construct (to give plasmid pAVh-beta-G-psi1) permitted the recombinant AAV genome to be rescued and replicate in the cell. (17 ref)

9/7/7

DIALOG(R)File 357:Derwent Biotechnology Abs

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0106673 DBA Accession No.: 90-09364

Production and expression of recombinant adeno-associated viruses harboring human beta-globin cDNA - adeno-associated virus expression in 293 cell culture; potential gene therapy for hemoglobinopathy diseases (conference abstract)

AUTHOR: Ohi S; Dixit M; Plonk S G

CORPORATE SOURCE: Meharry Medical College, Nashville, TN 37208, USA.
JOURNAL: FASEB J. (4, 7, A2288) 1990

CODEN: FAJOEC

LANGUAGE: English

ABSTRACT: 2 Plasmids that harbor human beta-globin (hbG) cDNA downstream of the P40 promoter of adeno-associated virus-2 (AAV2) DNA were constructed with the aim of using recombinant human parvo virus for hemoglobinopathy gene therapy. Plasmid pAVhbetaGpsi1 contains a partial hbG cDNA derived from JW102, whereas plasmid pAVdeltaKhpG contains a full-length hbG cDNA derived from plasmid pB6-6. Upon transfection, pAVhbetaGpsi1 expressed chimeric RNAs containing hbG sequences in human 293 cells. Recombinant genomes were rescued from both plasmids and replicated in the cell. This led to the production of infections recombinant AAV. When infected in 293 cells, the virus preparation resulted in efficient expression of hbG mRNAs in the cell. (3 ref)

9/7/9

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0086328 DBA Accession No.: 89-04319

Construction and characterization of recombinant adeno-associated virus genome containing human beta-globin cDNA - gene cloning and expression in human cell culture; potential sickle cell anemia or thalassemia gene therapy (conference abstract)

AUTHOR: Ohi S; Dixit M; Tillery M K

CORPORATE SOURCE: Department of Biochemistry and the Sickle Cell Center, Meharry Medical College, Nashville, TN 37208, USA.
JOURNAL: J Cell Biol. (107, 6, Pt.3, 304a) 1988

CODEN: JCBA3

LANGUAGE: English

ABSTRACT: The human parvo virus, adeno-associated virus, is a useful vector for cloning and expression of foreign genes. With the aim of construction of recombinant human parvo viruses containing either alpha-globin or beta-globin genes for gene therapy of hemoglobinopathies, such as sickle cell anemia and thalassemia, a cDNA sequence for human beta-globin was isolated and inserted downstream of the p40 promoter of adeno-associated virus. The beta-globin cDNA was excised from plasmid JW102 using S1 nuclease. The fragment was treated with Escherichia coli DNA-polymerase-I (EC-2.7.7), Klenow fragment and blunted ligated to plasmid pBR322, followed by cloning in Escherichia coli HB101. 1 Clone, plasmid pHbetaGS3, was amplified and the intact beta-globin cDNA region was excised on a HindIII-NHil fragment. The fragment was treated with Bal31 and blunt-end ligated to plasmid pAV2 downstream of the p40 promoter (HindIII site). From plasmid pAV2 a KpnI fragment was deleted (plasmid pAVdeltaKpn) to accommodate the foreign DNA. Expression of beta-globin under the control of p40 promoter was tested in human 293 cell culture and

pluripotent KS62 cell culture. (2 ref)

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0082125 DBA Accession No.: 89-00116

Expression and rescue of a nonselected marker from an integrated AAV vector
- chloramphenicol-acetyltransferase gene cloning in human cell culture
using adeno-associated virus vector

AUTHOR: Mendelson E; Smith M G; Carter B J

CORPORATE SOURCE: Laboratory of Molecular and Cellular Biology, National Institute of Diabetes, Digestive, and Kidney Diseases, Building 8, Room 304, National Institutes of Health, Bethesda, Maryland 20892, USA.

JOURNAL: Virology (166, 1, 154-65) 1988

CODEN: VIRLAX

LANGUAGE: English

ABSTRACT: Rep+ and rep- adeno-associated virus (AAV) vectors (plasmid pEM15 and plasmid pEM612 respectively) were constructed, containing a chloramphenicol-acetyltransferase (EC-2.3.1.28) (CAT) gene driven by the AAV p40 promoter, and a neo gene, driven by a herpes virus thymidine-kinase (EC-2.7.1.21) gene promoter. The vectors were transfected into a human 293 cell or HeLa cell culture, geneticin-resistant cells were selected, and cells were screened for CAT expression. With 293 cells, most rep- clones showed high CAT expression, but only 50% of rep+ clones expressed CAT, at a low level. With HeLa cells 25% of rep+ and rep- clones expressed CAT, some rep+ clones giving high yields. The rep+ vectors were also analyzed by rescue after superinfection with adeno virus and by Southern blot. AAV-CAT DNA could be rescued from 50% of HeLa cells but not from 293 cells. Non-rescue could be due to rearrangement of AAV termini or the rep gene. Western blot analysis showed low constitutive expression of rep protein in 1 293 cell clone and 2 HeLa cell clones. Thus, the AAV p40 promoter could drive expression of non-selected markers in integrated vectors, which could then be rescued. (26 ref)

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\$0.38 Estimated cost File357

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File 411:DIALINDEX(R)

DIALINDEX(R)

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 151: HealthSTAR _1975-1998/Dec
 155: MEDLINE(R) _1966-1999/Apr W1
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770: Beverage Marketing Research_1999/Feb

790: Tax Notes Today_1986-1999/Feb 22

791: State Tax Today_1991-1999/Feb 23

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\$0.16 0.124 DialUnits File411
 \$0.16 Estimated cost File411
 FTSNET 0.033 Hrs.

\$0.16 Estimated cost this search
 \$0.54 Estimated total session cost 0.167 DialUnits

File 342:Derwent Patents Citation Indx 1978-98/9907

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*File 342: Effective October 1, DialUnit rates adjusted for unrounding.

See HELP NEWS 342 for details.

Set Items Description

? help news 342

HELP NEWS 342 September 29, 1998

DERWENT PATENTS CITATION INDEX (DPCI)

As you may be aware, Dialog eliminated the rounding of DialUnits, effective 1 September 1998, in order to provide more equitable pricing for users conducting simple searches that incur a fractional DialUnit. This change in the pricing structure was in response to requests by Dialog customers.

In September, the elimination of DialUnit rounding significantly reduced the overall cost of searching DPCI because Derwent chose not to immediately revise their DialUnit pricing. To bring overall costs back in line with pre-September levels, Derwent has increased DialUnit rates effective 1 October 1998. New DialUnit prices for File 342 are as follows:

Non-Japanese Users	\$8.57
Japanese Users	\$9.43

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Executing TD511

S1 1418301 PY=1993:1999

18 AAV

102 ADENO

15118 ASSOCIATED

76 ADENO(W)ASSOCIATED

S2 80 AAV OR ADENO(W)ASSOCIATED

80 S2

0 ADENOASSOCIATED

S3 80 S2 OR ADENOASSOCIATED

S4 21150 SPECIFIC?

80 S3

21150 S4

S5 8 S3 AND S4

8 S5

1418301 S1

S6 0 S5 NOT S1

2923 PROMOTER

606 PROMOTERS

S7 3509 PROMOTER OR PROMOTERS

80 S3

3509 S7

1418301 S1

S8 0 S3 AND S7 NOT S1

0 S8

0 S6

S9 0 S8 NOT S6

S10 0 EXPRESSION(1A)CONTROL?

4848 EXPRESS?

296089 CONTROL?

S11 143 EXPRESS?(2N)CONTROL?

143 S11

80 S2

1418301 S1

0 S6

0 S9

S12 0 S11 AND S2 NOT (S1 OR S6 OR S9)

? t s2/7/1-10

2/7/1
 DIALOG(R)File 342:Derwent Patents Citation Indx

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 03298330 WPI Acc No. 98-557524/47

New vector containing therapeutic gene inserted between adeno-associated virus inverted terminal repeats - useful as safe gene therapy vectors

providing site-specific integration

Patent Assignee: (RICE-) IST RICERCHE BIOL MOLECOLARE ANGELETTI

Author (Inventor): CLELIBERTO G; COLLOCA S; FATTORI E; FIPALDINI C; LAMONICA N; MONCIOTTI A; PALOMBO F; PIERONI L; RECCHIA A; RIZZUTO G

Patent Family:

Patent No Kind Date Examiner Field of Search

WO 9845462 A1 981015 (BASIC)
AU 9870778 A 981030

Derwent Week (Basic): 9847

Priority Data: IT 97RM0200 (970408)

Applications: AU 9870778 (980408); WO 981T82 (980408)

Designated States

(National): AU; CA; CN; IL; JP; KR; MX; US
(Regional): AT; BE; CH; CY; DE; DK; ES; FI; FR; GB; GR; IE; IT; LU; MC; NL; PT; SE

Derwent Class: B04; D16

Int Pat Class: A61K-048/00; C12N-005/12

Number of Countries: 026

Number of Patents: 002

Number of Cited Patents: 004

Number of Cited Literature References: 005

Number of Citing Patents: 000

2/7/2

DIALOG(R)File 342:Derwent Patents Citation Indx

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03226721 WPI Acc No: 98-495836/42

Separating viruses of different sizes by filtration - particularly recovery of recombinant adeno-associated virus particles for gene therapy from infectious adenovirus(es)

Patent Assignee: (MEDI-) MEDIGENE AG

Author (Inventor): BOGEDAIN C; MAASS G; HOERER M

Patent Family:

Patent No Kind Date Examiner Field of Search

WO 9839420 A1 980911 (BASIC)
DE 197091186 A1 980911 C12N-001/2; C12N-007/2

Derwent Week (Basic): 9842

Priority Data: DE 10091186 (970306)

Applications: DE 10091186 (970306); WO 98EP1257 (980305)

Designated States

(National): AU; CA; JP; US
(Regional): AT; BE; CH; DE; DK; ES; FI; FR; GB; GR; IE; IT; LU; MC; NL; PT; SE

Derwent Class: A96; B04; D16

Int Pat Class: A61K-048/00; C12N-001/2; C12N-007/2

Number of Patents: 002

Number of Countries: 021

Number of Cited Patents: 007

Number of Cited Literature References: 003

Number of Citing Patents: 000

2/7/3

DIALOG(R)File 342:Derwent Patents Citation Indx

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03214195 WPI Acc No: 98-33205/29

Expression of polynucleotide(s) in mammals - by administering viral particles comprising recombinant adeno-associated virus to liver cells, used for, e.g. treating liver tumours

Patent Assignee: (SOMA-) SOMATIX THERAPY CORP; (UNIW) UNIV WASHINGTON

Author (Inventor): SNYDER R; DANOS O; COHEN L; KAY M; THOMPSON A R

Patent Family:

Patent No Kind Date Examiner Field of Search

WO 9824479 A1 980611 (BASIC)

AU 9855882 A 980629

Derwent Week (Basic): 9829

Priority Data: US 32506 (961202); US 882044 (970625)

Applications: WO 97US21398 (971202); AU 9855882 (971202)

Designated States

(National): AL; AM; AT; AU; AZ; BA; BB; BG; BR; BY; CA; CH; CN; CU; CZ; DE; DK; EE; ES; FI; GB; GE; GH; HU; ID; IL; IS; JP; KE; KG; KP; KR; KZ ; LC; LK; LR; LS; LT; LU; LV; MD; MG; MK; MN; MW; MX; NO; NZ; PL; PT; RO; RU; SD; SE; SG; SI; SK; SL; TJ; TM; TR; TT; UA; UG; US; UZ; VN; YU ; ZW

(Regional): AT; BE; CH; DE; DK; EA; ES; FI; FR; GB; GH; GR; IE; IT; KE; LS; LU; MC; MW; NL; OA; PT; SD; SE; SZ; UG; ZW

Derwent Class: B04; D16

Int Pat Class: A61K-048/00; C12N-007/01; C12N-015/10; C12N-015/63; C12N-015/86; C12Q-001/68

Number of Patents: 002

Number of Countries: 079

Number of Cited Patents: 001

Number of Cited Literature References: 002

Number of Citing Patents: 000

2/7/4

DIALOG(R)File 342:Derwent Patents Citation Indx

(C) 1999 Derwent Info Ltd. All rts. reserv.

03213179 WPI Acc No: 98-297948/26

Hybrid gene vector containing herpes and adeno-associated components - plus trans-gene for delivery to mitotic or non-mitotic cells, useful in gene therapy, provides stable expression and can accommodate large trans-genes

Patent Assignee: (GEHO) GEN HOSPITAL CORP; (SHRI-) SHRIVER CENT MENTAL

RETARDATION EUNICE
Author (Inventor): BREAKFIELD X O; JACOBY D R; SMITH F I

Patent Family:
WO 9821345 A1 980522 (BASIC)

Derwent Week (Basic): 9826

Priority Data: US 747919 (961112)

Applications: WO 97US20422 (971112); AU 9851999 (971112)

Designated States

(National): AL; AM; AT; AU; AZ; BA; BB; BG; BR; BY; CA; CH; CN; CU; CZ; DE; DK; EE; ES; FI; GB; GE; GH; HU; ID; IL; IS; JP; KE; KG; KP; KR; KZ ; LC; LK; LR; LS; LT; LU; LV; MD; MG; MK; MN; MW; MX; NO; NZ; PL; PT; RO; RU; SD; SE; SG; SI; SK; SL; TJ; TM; TR; TT; UA; UG; UZ; VN; YU; ZW (Regional): AT; BE; CH; DE; DK; EA; ES; FI; FR; GB; GH; GR; IE; IT; KE; LS; LU; MC; MW; NL; OA; PT; SD; SE; SZ; UG; ZW

Derwent Class: B04; D16

Int Pat Class: A01N-043/04; A61K-031/70

Number of Patents: 002

Number of Countries: 078

Number of Cited Patents: 000

Number of Cited Literature References: 003

Number of Citing Patents: 000

2/7/5

DIALOG(R)File 342:Derwent Patents Citation Indx

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03192851 WPI Acc No: 98-230428/20

New methods for gene therapy - by administering subcutaneously or topically a recombinant adeno-associated virus vector which expresses a gene of interest

Patent Assignee: (CELL-) CELL GENESYS INC
Author (Inventor): SNYDER R; DANOS O; MCARTHUR J; MULLIGAN R

Patent Family:

WO 9813070 A1 980402 (BASIC)
AU 9747367 A 980417

Derwent Week (Basic): 9820

Priority Data: US 26638 (960925)

Applications: AU 9747367 (970925); WO 97US16929 (970925)

Designated States

(National): AL; AM; AT; AU; AZ; BA; BB; BG; BR; BY; CA; CH; CN; CU; CZ; DE; DK; EE; ES; FI; GB; GE; GH; HU; ID; IL; IS; JP; KE; KG; KP; KR; KZ ; LC; LK; LR; LS; LT; LU; LV; MD; MG; MK; MN; MW; MX; NO; NZ; PL; PT; RO; RU; SD; SE; SG; SI; SK; SL; TJ; TM; TR; TT; UA; UG; US; UZ; VN; YU ; ZW (Regional): AT; BE; CH; DE; DK; EA; ES; FI; FR; GB; GH; GR; IE; IT; KE;

LS; LU; MC; MW; NL; OA; PT; SD; SE; SZ; UG; ZW

Derwent Class: B04; D16
Int Pat Class: A61K-009/08; A61K-048/00

Number of Patents: 002

Number of Countries: 079

Number of Cited Patents: 002

Number of Cited Literature References: 002

Number of Citing Patents: 000

2/7/6

DIALOG(R)File 342:Derwent Patents Citation Indx

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03191639 WPI Acc No: 98-193255/17

Novel adeno-associated viral vectors - for liver specific delivery of therapeutic molecule

Patent Assignee: (CHIR) CHIRON CORP; (INDV) UNIV INDIANA

Author (Inventor): SRIJASTAVA A; PONNAZHAGAN S; CHLOEMER R H; WANG X; YODER

M C; ZHOU S; ESCOBEDO J; DWARKI V

Patent Family:

Patent No Kind Date

WO 9809524 A1 980312 (BASIC)

Derwent Week (Basic): 9817

Priority Data: US 25616 (960906); US 25649 (960911)

Applications: WO 97US15453 (970902)

Designated States

(National): CA; JP

(Regional): AT; BE; CH; DE; DK; ES; FI; FR; GB; GR; IE; IT; LU; MC; NI;

PT; SE

Derwent Class: B04; D16

Int Pat Class: A01N-043/04; A61K-031/70

Number of Patents: 001

Number of Countries: 019

Number of Cited Patents: 001

Number of Cited Literature References: 007

Number of Citing Patents: 000

2/7/7

DIALOG(R)File 342:Derwent Patents Citation Indx

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03182693 WPI Acc No: 98-377242/32

Transfection of primate pluripotent haematopoietic stem cells with an adeno-associated viral vector - useful for expressing e.g. a therapeutic protein in pluripotent cells for the treatment of diseases such as sickle cell anaemia

Patent Assignee: (INTR-) INTROGENE BV

Author (Inventor): EINERHAND M P W; VALERIO D

Patent Family:		Patent No	Kind Date	Examiner	Field of Search
	WO 9824924	A1	980611 (BASIC)		
Derwent Week (Basic):	9832				
Priority Data:	EP 96203444 (961205)				
Applications:	WO 97NL631 (971119)				
Designated States					
(National): AL; AM; AT; AU; AZ; BA; BB; BG; BR; BY; CA; CH; CN; CU; CZ; DE; DK; EE; ES; FI; GB; GE; GH; HU; ID; IL; IS; JP; KE; KG; KP; KR; KZ ;LC; LK; LR; LS; LT; LU; LV; MD; MG; MK; MN; MW; MX; NO; NZ; PL; PT; RO; RU; SD; SE; SG; SI; SK; SL; TJ; TM; TR; TT; UA; UG; US; UZ; VN; YU ;ZW	2/7/9	DIALOG(R)File 342:Derwent Patents Citation Indx			
(Regional): AT; BE; CH; DE; DK; EA; ES; FI; FR; GB; GH; GR; IE; IT; KE; LS; LU; MC; MW; NL; OA; PT; SD; SE; SZ; UG; ZW		(c) 1999 Derwent Info Ltd. All rts. reserv.			
Derwent Class: B04; D16		03182340 WPI Acc No: 98-3622773/31			
Int'l Pat Class: A61K-048/00; C12N-005/10		High efficiency packaging of recombinant adeno-associated virus vector - containing at least one AAV split-cap, AAV rep78 or AAV rep52 split-packaging gene, used for transfecting mammalian cells			
Number of Patents: 001		Patent Assignee: (TARG-) TARGETED GENETICS CORP			
Number of Countries: 079		Author (Inventor): ALLEN J M; STEPAN A M; QUINTON T J; LUPTON S D			
Number of Cited Patents: 003		Patent Family:	Patent No	Kind Date	Examiner Field of Search
Number of Cited Literature References: 003			WO 9827204	A2 980625 (BASIC)	
Number of Citing Patents: 000			Derwent Week (Basic):	9831	
			Priority Data:	US 41609 (961218)	
			Applications:	WO 97US23247 (971212)	
Designated States		Designated States	(National): AL; AM; AT; AU; AZ; BA; BB; BG; BR; BY; CA; CH; CN; CU; CZ; DE; DK; EE; ES; FI; GB; GE; GH; GM; HU; ID; IL; IS; JP; KE; KG; KP; KR ;KZ; LC; LK; LR; LS; LT; LU; LV; MD; MG; MK; MN; MW; MX; NO; NZ; PL; PT; RO; RU; SD; SE; SG; SI; SK; SL; TJ; TM; TR; TT; UA; UG; US; UZ; VN ;YU; ZW		
		(Regional): AT; BE; CH; DE; DK; EA; ES; FI; FR; GB; GH; GM; GR; IE; IT; KE; LS; LU; MC; MW; NL; OA; PT; SD; SE; SZ; UG; ZW			
		Derwent Class:	B04; D16	Int'l Pat Class:	C12N-015/00
		Number of Patents:	001	Number of Countries:	080
		Number of Cited Patents:	004	Number of Cited Literature References:	001
		Number of Citing Patents:	000		
2/7/8	DIALOG(R)File 342:Derwent Patents Citation Indx				
	(c) 1999 Derwent Info Ltd. All rts. reserv.				
03182343 WPI Acc No: 98-3622776/31					
Polynucleotide comprising adeno-associated virus, useful for gene therapy - comprise an AAV packaging site containing promoter and site-specific recombination sequences for activation by recombinase					
Patent Assignee: (TARG-) TARGETED GENETICS CORP					
Author (Inventor): BURSTEIN H		Patent Family:	Patent No	Kind Date	Examiner Field of Search
			WO 9827207	A1 980625 (BASIC)	
			Derwent Week (Basic):	9831	
			Priority Data:	US 41689 (961218)	
			Applications:	WO 97US23018 (971212)	
Designated States		Designated States	(National): AL; AM; AT; AU; AZ; BA; BB; BG; BR; BY; CA; CH; CN; CU; CZ; DE; DK; EE; ES; FI; GB; GE; GH; GM; GW; HU; ID; IL; IS; JP; KE; KG; KP ;KR; KZ; LC; LK; LR; LS; LT; LU; LV; MD; MG; MK; MN; MW; MX; NO; NZ; PL; PT; RO; RU; SD; SE; SG; SI; SK; SL; TJ; TM; TR; TT; UA; UG; US; UZ ;VN; YU; ZW		
		(Regional): AT; BE; CH; DE; DK; EA; ES; FI; FR; GB; GH; GM; GR; IE; IT; KE; LS; LU; MC; MW; NL; OA; PT; SD; SE; SZ; UG; ZW			
Derwent Class:	B04; D16	Derwent Class:	C07K-014/015; C07K-014/47; C12N-005/10; C12N-007/01;	Int'l Pat Class:	
DIALOG(R)File 342:Derwent Patents Citation Indx					
(c) 1999 Derwent Info Ltd. All rts. reserv.					
03162607 WPI Acc No: 97-0998 96/09					
Expressing gene prod. in muscle using adeno-associated viral vector - providing efficient, long-term expression and able to infect non-dividing cells					
Patent Assignee: (UYNC-) UNIV NORTH CAROLINA					
Author (Inventor): XIAO X; SAMULSKI R J					

Patent Family:

Patent No	No	Kind Date	Examiner	Field of Search
WO 9640272 A1 961219 (BASIC)				
AU 9662686 A 961230				
EP 844887 A1 980603				
Derwent Week (Basic): 9709				
Priority Data: US 487005 (950607)				
Applications: AU 9662686 (960605); EP 96921468 (960605); WO 96USS9879 (960605)				

Designated States

(National): AU; CA; IL; JP
(Regional): AT; BE; CH; DE; DK; ES; FI; FR; GB; GR; IE; IT; LI; LU; MC; NL; PT; SE

Derwent Class: B04; D16

Int Pat Class: A61K-048/00

Number of Patents: 003

Number of Countries: 022

Number of Cited Patents: 000

Number of Cited Literature References: 001

Number of Citing Patents: 001

CITING PATENTS

Family Member	Citing Patent Cat	WPI Acc No	Assignee/Inventor
WO 9640272 A1 US 5846528 A 97-385339/35 (AVIG-) AVIGEN INC/ PODSAKOFF G M; KURTZMAN G J			

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23feb99 09:51:48 User208669 Session D1383.6
\$7.77 0.856 DialUnits File342
\$0.00 20 Type(s) in Format 6
\$57.30 10 Type(s) in Format 7
\$57.30 30 Types
\$65.07 Estimated cost File342
FTSNET 0.033 Hrs.

\$65.07 Estimated cost this search
\$65.61 Estimated total session cost 1.024 DialUnits
Logoff. level 99.01.29 D 09:51:48

? b 155

23feb99 09:28:24 User208669 Session D1383.1

\$0.19 0.059 DialUnits File1

\$0.19 Estimated cost File1

FTSNET 0.002 Hrs.

\$0.19 Estimated cost this search

\$0.19 Estimated total session cost 0.059 DialUnits

expressed in adeno-associated virus vectors *in vitro*. (51 Refs.)

6/7/8

DIALOG(R)File 155: MEDLINE(R)

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07296175 92410609

Modulation of the cellular phenotype by integrated adeno-associated virus.

Winocour E, Puzis L; Etkin S; Koch T; Danovitch B; Mendelson E; Shaulian E; Karby S; Lavi S

Department of Molecular Genetics and Virology, Weizmann Institute of Science, Rehovot, Israel.

Virology (UNITED STATES) Sep 1992, 190 (1) p316-29, ISSN 0042-6822

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Set Items Description

File 155: MEDLINE(R) 1966-1999/Apr W1

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Set Items Description

Set Items Description

S1 2337031 PY=1993:1999

S2 761 AAV OR ADENO(W)ASSOCIATED

S3 770 S2 OR ADENOASSOCIATED

S4 867589 SPECIFIC?

S5 222 S3 AND S4

S6 73 S5 NOT S1

S7 63088 PROMOTER OR PROMOTERS

S8 49 S3 AND S7 NOT S1

S9 33 S8 NOT S6

S10 0 EXPRESSION(1A)CONTROL?

S11 7846 EXPRESS?(2N)CONTROL?

? ts6/7/6 8 9 14 18 24 36

6/7/6

DIALOG(R)File 155: MEDLINE(R)

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07333400 93043547

Adeno-associated virus vectors.

Carter BJ

Targeted Genetics Corporation, Seattle, Washington.

Curr Opin Biotechnol (ENGLAND) Oct 1992, 3 (5) p533-9, ISSN 0958-1669

Journal Code: A92

Languages: ENGLISH

Document type: JOURNAL ARTICLE, REVIEW, TUTORIAL

Adeno-associated virus is a human Parvovirus that integrates its DNA genome into host cell chromosomes with very high efficiency. This suggests that adeno-associated virus may be a useful vector for human gene therapy. Interest in adeno-associated virus vectors increased greatly in the last year following reports that adeno-associated virus genome integration may be site specific and occur at preferred sites in the human genome. Several genes relevant to the treatment of genetic or infectious diseases have been

6/7/9

DIALOG(R)File 155: MEDLINE(R)

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07288855 92287906

Gene transfer in human lymphocytes using a vector based on adeno-associated virus.

NOS

Muro-Cacho CA; Samulski RJ; Kaplan D

Institute of Pathology, Case Western Reserve University, Cleveland, Ohio 44106.

J Immunother (UNITED STATES) May 1992, 11 (4) p231-7, ISSN 1053-8550

Journal Code: AZ0

Contract/Grant No.: AI-28923, AI, NIAID; DK-42701, DK, NIDDK; AI-25530, AI, NIAID

Languages: ENGLISH

Document type: JOURNAL ARTICLE

Adeno-associated virus is a nonpathogenic, dependent parvovirus that integrates at a specific site in human chromosome 19. We have used the inverted terminal repeats of the virus, which mediate integration, to establish a vector for gene transfer in human lymphocytes. A neomycin resistance gene has been stably introduced into nontransformed human T-cell clones and a subsequent analysis of the functional properties of the infected clone revealed no detectable alterations. Rescue and replication of the wild-type virus was accomplished with adenovirus superinfection; however, the vector was not rescued and did not replicate by this procedure, indicating the stability of the integrated vector and demonstrating an additional level of safety incorporated in its construction. An adeno-associated virus-based vector represents an alternative to retroviruses for gene therapy in lymphocytes.

6/7/14

DIALOG(R)File 155:MEDLINE(R)

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06954089 92037558

Targeted integration of adeno-associated virus (AAV) into human chromosome 19 [published erratum appears in EMBO J 1992 Mar;11(3):1228] Samulski RJ; Zhu X; Xiao X; Brook JD; Housman DE; Epstein N; Hunter LA Department of Biological Sciences, University of Pittsburgh, PA 15260. EMBO J (ENGLAND) Dec 1991, 10 (12) p3941-50, ISSN 0261-4189 Journal Code: EMB Contract/Grant No.: AI 25530-03, AI, NIAID

Languages: ENGLISH

Document type: JOURNAL ARTICLE

A key feature in adeno-associated virus (AAV) replication is efficient integration of the viral genome into host cell DNA to establish latency when helper virus is absent. The steps involved in this process remain largely uncharacterized, even though AAV integration was first documented 20 years ago. Using a protein-DNA binding method we isolated AAV-cellular junction DNA sequences. The cellular component hybridized to a single restriction fragment in the virus-free parental cell line, and also co-migrated with AAV-specific sequences in numerous latently infected cell lines. Analysis of somatic cell hybrids indicated that this cellular sequence maps to the distal portion of the q arm of human chromosome 19. In situ hybridization of AAV DNA to chromosomes from latently infected cells confirms the physical location of AAV integrations to be q13.4-ter of

chromosome 19. Sequence analysis of several independent integration sites shows breakpoints occurring within a 100 bp cellular region. This non-pathogenic parvovirus thus appears to establish viral latency by integrating its DNA specifically into one chromosomal region. Such specific integration is so far unique among the eukaryotic DNA viruses. The incorporation of site-specific integration into AAV vector schemes should make this vector system attractive for human gene therapy approaches.

6/7/18

DIALOG(R)File 155:MEDLINE(R)

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06829588 92052179

Isolation of a candidate repressor/activator, NF-E1 (YY-1, delta), that binds to the immunoglobulin kappa 3' enhancer and the immunoglobulin heavy-chain mu E1 site. Park K; Atchison ML

Department of Animal Biology, University of Pennsylvania, School of Veterinary Medicine, Philadelphia 19104. Proc Natl Acad Sci U S A (UNITED STATES) Nov 1 1991, 88 (21) p9804-8, ISSN 0027-8424 Journal Code: PV3 Contract/Grant No.: RO1 GM42415, GM, NIGMS Languages: ENGLISH Document type: JOURNAL ARTICLE

We have determined that the developmental control of immunoglobulin kappa 3' enhancer (Kappa E3') activity is the result of the combined influence of positive- and negative-acting elements. We show that a central core in the kappa E3' enhancer is active at the pre-B-cell stage but is repressed by flanking negative-acting elements. The negative-acting sequences repress enhancer activity in a position- and orientation-independent manner at the pre-B-cell stage. We have isolated a human cDNA clone encoding a zinc finger protein (NF-E1) that binds to the negative-acting segment of the kappa E3' enhancer. This protein also binds to the immunoglobulin heavy-chain enhancer mu E1 site. NF-E1 is encoded by the same gene as the YY-1 protein, which binds to the adeno-associated virus P5 promoter. NF-E1 is also the human homologue of the mouse delta protein, which binds to ribosomal protein genes. The predicted amino acid sequence of this protein contains features characteristic of transcriptional activators as well as transcriptional repressors. Cotransfection studies with this cDNA indicate that it can repress basal promoter activity. The apparent dual function of this protein is discussed.

6/7/24

DIALOG(R)File 155:MEDLINE(R)

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06626755 90192777

Site-specific integration by adeno-associated virus.

Kotin RM; Siniscalco M; Samulski RJ; Zhu XD; Hunter L; Laughlin CA;

McLaughlin S; Muzychka N; Rocchi M; Berns KJ
 Hearst Microbiology Research Center, Department of Microbiology, Cornell University Medical College, New York, NY 10021.
 Proc Natl Acad Sci U S A (UNITED STATES) Mar 1990, 87 (6) p2211-5,
 ISSN 0027-8424 Journal Code: PV3
 Contract/Grant No.: AI22251, AI, NIAID; GM37090, GM, NIGMS; AI25530, AI,
 NIAID; +

Languages: ENGLISH

Document type: JOURNAL ARTICLE

Cellular sequences flanking integrated copies of the adeno-associated virus (AAV) genome were isolated from a latently infected clonal human cell line and used to probe genomic blots derived from an additional 21 independently derived clones of human cells latently infected with AAV. In genomic blots of uninfected human cell lines and of primary human tissue, each flanking sequence probe hybridized to unique bands, but in 15 of the 22 latently infected clones the flanking sequences hybridized not only to the original fragments but also to a total of 36 additional species. AAV probes also hybridized to 22 of these new bands, representing 11 of the 15 positive clones, but never to the fragment characteristic of uninfected cell DNA. From these data we conclude that the AAV genome preferentially integrates into a specific region of the cellular genome. We have determined that the integration site is unique to chromosome 19 by somatic cell hybrid mapping, and this sequence has been isolated from uninfected human DNA.

6/7/36

DIALOG(R)File 155:MEDLINE(R)

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06116071 87036912

Latent infection of KB cells with adeno-associated virus type 2.

Laughlin CA; Cardellichio CB; Coon HC
 J Virol (UNITED STATES) Nov 1986, 60 (2) p515-24, ISSN 0022-538X

Journal Code: KCV

Contract/Grant No.: R01 AI/CIA 19934, AI, NIAID

Languages: ENGLISH

Document type: JOURNAL ARTICLE

Adeno-associated virus (AAV) is a prevalent human virus whose replication requires factors provided by a coinfecting helper virus. AAV can establish latent infections *in vitro* by integration of the AAV genome into cellular DNA. To study the process of integration as well as the rescue of AAV replication in latently infected cells after superinfection with a helper virus, we established a panel of independently derived latently infected cell clones. KB cells were infected with a high multiplicity of AAV in the absence of helper virus, cloned, and passaged to dilute out input AAV genomes. AAV DNA replication and protein synthesis were rescued from more than 10% of the KB cell clones after superinfection with adenovirus type 5 (Ad5) or herpes simplex virus types 1 or 2. In the absence of helper virus,

there was no detectable expression of AAV-specific RNA or proteins in the latently infected cell clones. Ad5 superinfection also resulted in the production of infectious AAV in most cases. All mutant adenoviruses tested that were able to help AAV DNA replication in a coinfection were also able to rescue AAV from the latently infected cells, although one mutant, Ad5hr6, was less efficient at AAV rescue. Analysis of high-molecular-weight cellular DNA indicated that AAV sequences were integrated into the cell genome. The restriction enzyme digestion patterns of the cellular DNA were consistent with colinear integration of the AAV genome, with the viral termini present at the cell-virus junction. In addition, many of the cell lines appeared to contain head-to-tail concatemers of the AAV genome. The understanding of the integration of AAV DNA is increasingly important since AAV-based vectors have many advantages for gene transduction *in vitro* and *in vivo*.

?t s97/4-6 8 12 16 18 21 26 31

9/7/4

DIALOG(R)File 155:MEDLINE(R)

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 07382011 92348451

Chromosomal localization and organization of the murine genes encoding the beta subunits (AIC2A and AIC2B) of the interleukin 3, granulocyte/macrophage colony-stimulating factor, and interleukin 5 receptors.

Gorman DM, Itoh N, Jenkins NA, Gilbert DJ, Copeland NG, Miyajima A

Department of Molecular Biology, DNAX Research Institute of Molecular and Cellular Biology, Palo Alto, California 94304.

J Biol Chem (UNITED STATES) Aug 5 1992, 267 (22) p15842-8, ISSN 0021-9258 Journal Code: HIV
 Contract/Grant No.: N01-CO-74101, CO, NCI
 Languages: ENGLISH
 Document type: JOURNAL ARTICLE

Chromosomal genes for two mouse homologous beta subunits (AIC2A and AIC2B) of the interleukin-3, granulocyte/macrophage colony-stimulating factor, and interleukin-5 receptors were characterized. Both AIC2A and AIC2B genes were present on a 250-kilobase M_{sp} restriction fragment and were mapped on murine chromosome 15 (these loci were provisionally designated as IL3rb-1 (AIC2A) and IL3rb-2 (AIC2B)), closely linked to the c-sis locus. Both genes consist of 14 exons and span about 28 kb each. The major transcription initiation sites of both genes were mapped at 194 bp from the initiation codon. These genes are 95% identical up to 700 bp from the transcription initiation sites. Potential recognition sequences for hemopoietic transcription factors including GATA-1 and PU.1 in addition to a TATA-like sequence are present in the 5'-flanking region. A stretch of 20 bp including the initiation site is homologous to the corresponding region of the erythropoietin receptor and the interleukin-7 receptor genes and to the initiator sequence of the adeno-associated virus P5 promoter,

suggesting a possible role in transcription initiation. Comparison of the exon/intron boundaries of AIC2A and AIC2B genes with those of other members of the cytokine receptor superfamily reveals a conserved evolutionary structure. Isolation of various forms of AIC2 cDNAs reveals differential splicing of the transcripts.

9/7/5

DIALOG(R)File 155:MEDLINE(R)

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07330679 90329218

The recombinant human parvoviruses for gene therapy of hemoglobinopathies.

Dixit M; Tillery MK; Plonk SG; Ohi S

Department of Biochemistry, Meharry Medical College, Nashville, TN 37208.
SAAS Bull Biochem Biotechnol (UNITED STATES) Jan 1990, 3 p63-8,

Journal Code: ALK

Contract/Grant No.: HL01989, HL, NHLBI; HL38737, HL, NHLBI

Languages: ENGLISH

Document type: JOURNAL ARTICLE

Towards a goal of using adeno-associated viruses (AAV), the human parvovirus, as the gene transfer vector for gene therapy of hemoglobinopathies, the human beta-globin (*h* beta G) cDNA was ligated downstream of the P40 promoter of AAV type 2 (AAV2) genome. Transfection via electroporation of the construct into human 293 cells (embryonal kidney cell line) resulted in expression of the cloned *h* beta G cDNA, as evidenced by the synthesis of transcripts hybridizable to *h* beta G probe. The transfection led to the recombinant genome to be excised out of the plasmid and replicate in the cell, followed by production of the recombinant AAV that harbors *h* beta G cDNA.

9/7/6

DIALOG(R)File 155:MEDLINE(R)

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07302580 93099882

Characterization of a preferred site on human chromosome 19q for integration of adeno-associated virus DNA by non-homologous recombination.
Kotin RM; Linden RM; Berns KJ
Molecular Hematology Branch, National Institutes of Health, Bethesda, MD 20892.

EMBO J (ENGLAND) Dec 1992, 11 (13) p5071-8, ISSN 0261-4189

Journal Code: EMB

Contract/Grant No.: AI 222251, AI, NIAID

Languages: ENGLISH

Document type: JOURNAL ARTICLE

The human parvovirus, adeno-associated virus (AAV), has been shown to integrate preferentially into human chromosome 19 q13.3-qter. The human target sequence for AAV integration (AAV5) was cloned and sequenced. By

analysis of the proviral junctions it was determined that integration of the AAV DNA occurred via a non-homologous recombination pathway although there were either four or five identical nucleotides at the junctions. Integration was a multistep concerted process that resulted in cellular sequence rearrangements. The sequence of the integration locus was analyzed for possible recombination signals. Direct repeats at a much greater than random occurrence were found distributed non-uniformly throughout the AAVS1 sequence. A CpG island containing transcription factor binding site elements is suggestive of a TATA-less promoter. Evidence for transcriptional activity was provided by PCR amplification of reverse transcribed RNA.

9/7/8

DIALOG(R)File 155:MEDLINE(R)

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07295326 92392571

Gene expression from adeno-associated virus vectors in airway epithelial cells.

Flotte TR; Solow R; Owens RA; Afione S; Zeitlin PL; Carter BJ
Laboratory of Molecular and Cellular Biology, National Institute of Diabetes, Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD 20892.Am J Respir Cell Mol Biol (UNITED STATES) Sep 1992, 7 (3) p349-56,
ISSN 1044-1549 Journal Code: AOB

Languages: ENGLISH

Document type: JOURNAL ARTICLE

Lung diseases such as cystic fibrosis (CF) might be treated by gene therapy using viral vectors delivered to the airway. One potential vector is the defective human parvovirus, adeno-associated virus (AAV). We examined the AAV p5 transcription promoter for gene expression in immortalized cell lines derived from the airway (IB3-1) or pancreas (CFPAC-1) of CF patients. AAV vectors expressing the prokaryotic genes cat (pAAVp5cat) or neo (pAAVp5neo) from the p5 promoter were evaluated after introduction into IB3-1 or CFPAC-1 cells by lipofection. In transient assays in both cell lines, the cat gene was expressed 5- to 10-fold more efficiently from the p5 promoter than from a simian virus 40 early gene promoter (pSVcat). IB3-1 cells were transformed stably to geneticin resistance by pAAVp5neo at a 5-fold higher efficiency than by an SVneo vector. The AAV inverted terminal repeat (ITR) region immediately upstream of the p5 promoter appears to have an enhancer effect and the promoter also contains a CREB site which confers a response to forskolin. In IB3-1 cells, expression of the cat gene from a p5 promoter was decreased about 5-fold by deletion of both the upstream ITR and the CREB site. The AAVp5neo vector was also packaged into AAV particles and used to infect IB3-1 cells as a transducing virus. Under these conditions, 60 to 70% of the cells could be stably transformed to geneticin resistance. Thus, AAV transducing vectors appear to be a highly efficient delivery system for stable integration and

expression of genes in cultured airway epithelial cells.

Languages: ENGLISH

Document type: JOURNAL ARTICLE

With the goal of using adeno-associated viruses (AAV) as the gene-transfer vector for gene therapy of hemoglobinopathies, human beta-globin cDNA was ligated downstream from the P40 promoter of the AAV type-2 (AAV2) genome. To circumvent difficulties of cloning DNA containing palindromic sequences, two of which exist in the termini of AAV genome, a step-wise approach handling one palindrome at a time was devised to construct the chimeric expression vector. Electroporation of the construct into human 293 cells (embryonal kidney cell line) resulted in expression of the cloned human beta-globin cDNA, as evidenced by the synthesis of transcripts hybridizable to human beta-globin cDNA probe. Addition of the 3'-end region of AAV DNA that contains both the transcription termination signal and origin of DNA replication for AAV to the construct permitted the recombinant AAV genome to be rescued and replicate in the cell.

9/7/12
DIALOG(R)File 155:MEDLINE(R)

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06952402 92009221

Construction and expression of a recombinant adeno-associated virus that harbors a human beta-globin-encoding cDNA.
Dixit M; Webb MS; Smart WC; Ohi S

Department of Biochemistry, School of Medicine, Meharry Medical College, Nashville, TN.
Gene (NETHERLANDS) Aug 15 1991, 104 (2) p253-7, ISSN 0378-1119

Journal Code: FOP
Contract/Grant No.: HL019898, HL, NHLBI; HL38737, HL, NHLBI

Languages: ENGLISH

Document type: JOURNAL ARTICLE

Towards a goal of using recombinant adeno-associated viruses (AAV) for the gene therapy of hemoglobinopathies we had previously constructed plasmid pAV h beta G psi 1, which contained a human beta-globin-encoding cDNA (HBB) downstream from the P40 promoter of AAV2 DNA [Ohi et al., Gene 89 (1990) 279-282]. Transfection of the plasmid into human 293 cells (embryonal kidney cell line) resulted in the expression of HBB at the mRNA level as well as rescue and replication of the recombinant AAV genome (Ohi et al., ibid.). The present study demonstrates that the replicated recombinant DNA was packaged into an intact virion by transcomplementation with pAV2 or the defective helpers, pAV delta Bam or pAVXB. The recombinant virus could be isolated by equilibrium CsCl density gradient, the density of which was about 1.4 g/cm³. The defective helpers are used to produce wild-type AAV-free recombinant AAV. The recombinant AAV were infectious and expressed chimeric mRNAs containing the HBB sequence in virus-infected 293, KB (oral epidermoid carcinoma cell line) and K562 (human erythroleukemia cell line) cells. The importance of the infectivity and expression of the recombinant AAV in hematopoietic cells is discussed in the context of gene therapy of hemoglobinopathies.

9/7/16
DIALOG(R)File 155:MEDLINE(R)

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06634298 90323629

Construction and replication of an adeno-associated virus expression vector that contains human beta-globin cDNA.
Ohi S; Dixit M; Tillery MK; Plonk SG
Department of Biochemistry, School of Medicine, Meharry Medical College, Nashville, TN 37208.
Gene (NETHERLANDS) May 14 1990, 89 (2) p279-82, ISSN 0378-1119

Journal Code: FOP
Contract/Grant No.: HL019898, HL, NHLBI; HL38737, HL, NHLBI
Nashville, TN 37208.

Languages: ENGLISH

Document type: JOURNAL ARTICLE

We used rep+ and rep- recombinant AAV-plasmid vectors containing the nonselectable marker chloramphenicol acetyltransferase (CAT) driven by the AAV p40 promoter, and having a selectable marker, neo, inserted in the plasmid genome, and driven by a herpesvirus thymidine kinase gene promoter. Each vector was transfected into human 293 cells or HeLa cells and the neo gene was used to select geneticin-resistant (genr) cells containing integrated vectors. The genr cells were then screened for expression of the unselected marker CAT. For 293 cells, most clones from the rep- vector gave high CAT expression whereas only 50% of those from the rep+ vector expressed CAT, generally at low level. For HeLa cells about 25% of the clones derived from either the rep+ or rep- vector expressed CAT, and several clones from the rep+ vector gave very high yields. We also analyzed integrated rep+ vectors by rescue after superinfection with adenovirus and by Southern blotting. The AAV-CAT genome could be rescued from 50% of HeLa cell clones but not from 293 cell clones. Lack of rescuable reflected rearrangement of the AAV genome termini or the rep gene. Western blotting showed low level constitutive expression of rep protein in one 293 cell clone and two HeLa cell clones. Thus, the AAV p40 promoter (as well as p5

and p19) can function in integrated vectors to express unselected markers which can subsequently be rescued. Expression and rescue depended upon several parameters including the cell type, the initial structure of the vector (rep+ or rep-) but not continued expression of rep, and possibly global effects of the surrounding chromatin.

9/7/21

DIALOG(R)File 155:MEDLINE(R)

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06265856 86310795

Adeno-associated virus vector for high-frequency integration, expression, and rescue of genes in mammalian cells.

Tratschin JD; Miller LL; Smith MG; Carter BJ

Mol Cell Biol (UNITED STATES) Nov 1985, 5 (11) p3251-60, ISSN 0270-7306 Journal Code: NGY

Languages: ENGLISH

Document type: JOURNAL ARTICLE

We describe the construction of an adeno-associated virus (AAV) vector in which the coding sequence of the prokaryotic gene neo is expressed under the control of the major AAV promoter p40. This AAV-neo vector allowed stable expression of neo as a dominant selective marker in mammalian cells by selection of cells which were resistant to the antibiotic geneticin (G418). When the vector was introduced into human (293 or HeLa) cell lines by a DNA transfection procedure, stable geneticin-resistant colonies were obtained. When the vector was first packaged into AAV particles and then introduced into cells via particle infection, geneticin-resistant cells were obtained at higher frequencies than those obtained by DNA transfection. In geneticin-resistant cells the AAV-neo vector was integrated at low copy number and could be rescued by subsequent infection with wild-type AAV and the helper adenovirus or, in some cases, by infection with adenovirus alone. The rescued AAV-neo vector could then be recovered as amplified unintegrated DNA from a Hirt lysate. These results demonstrate that AAV can be used as a transducing viral vector for stable integration and expression of a foreign gene in mammalian cells. The high frequency of integration and the ability to rescue the integrated vector suggest that this vector system may be useful for selecting genes from cDNA libraries. This vector may also be useful for introduction of genes into cells which are refractory to transfection in procedures such as those involving the use of CapO4 or DEAE-dextran.

Virology (UNITED STATES) Sep 1987, 160 (1) p38-47, ISSN 0042-6822
Journal Code: XEA
Languages: ENGLISH
Document type: JOURNAL ARTICLE

We used a recombinant plasmid containing an adeno-associated virus (AAV) genome to construct several vectors which express the gene for chloramphenicol acetyltransferase (CAT). We transfected four different AAV-CAT vectors into human 293 (adenovirus-transformed) cells and analyzed CAT activity. We show that, for vectors using the AAV p40 and p19 promoter, the chimeric AAV-CAT transcripts began from the correct 5' position but the basal level of CAT expression depended in part on the structure of the transcript. We also examined the effects of coinfection of the cells with the helper adenovirus or cotransfection with a plasmid which expressed the adenovirus translational control RNA, VA1 RNA. Cotransfection with plasmids containing the gene for VA1 RNA resulted in elevated levels of CAT activity. VA1 RNA stimulated translation of the chimeric mRNA. However, in two cases, the VA1 RNA apparently decreased the level of mRNA. These results suggest that in addition to its function in translation, VA1 RNA acts at a second site to alter cytoplasmic accumulation of some mRNAs. Infection with adenovirus increased CAT activity several-fold by increasing the cytoplasmic levels of the chimeric AAV-CAT transcript. When the CAT gene is inserted down stream of the AAV intron, adenovirus and not VA1 RNA alone increased CAT activity by promoting accumulation of a spliced transcript.

9/7/31

DIALOG(R)File 155:MEDLINE(R)

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05368677 88288213

Cloning of the human thyrotropin beta-subunit gene and transient expression of biologically active human thyrotropin after gene transfection.

Wondisford FE; Usala SJ; DeCherney GS; Castren M; Radovick S; Gyves PW; Trempe JP; Kerfoot BP; Nikodem VM; Carter BJ; et al
Molecular, Cellular and Nutritional Endocrinology Branch, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, Maryland 20892.Mol Endocrinol (UNITED STATES) Jan 1988, 2 (1) p32-9, ISSN 0888-8809
Journal Code: NGZ
Languages: ENGLISH
Document type: JOURNAL ARTICLE

A 17 kilobase pair fragment of DNA containing the human TSH (hTSH) beta-subunit gene was isolated from a human leukocyte genomic library. Using a 621 base pair human CG alpha-subunit cDNA and a 2.0 kilobase pair genomic fragment of hTSH beta containing both coding exons, we constructed hCG alpha and hTSH beta expression vectors containing either the early promoter of simian virus 40 or the promoters of adeno-associated virus. West MJ; Trempe JP; Tratschin JD; Carter BJ

Cotransfection of two adeno-associated virus vectors, each containing one subunit of hTSH, together with a plasmid containing the adenovirus VA RNA genes produced hTSH as well as free human alpha- and TSH beta-subunits in an adenovirus transformed human embryonal kidney cell line (293). The levels of protein expression in this system were 10- to 100-fold greater than that found in a simian virus transformed monkey kidney cell line (COS) using vectors containing the early promoter of simian virus 40. The hTSH synthesized in 293 cells was glycosylated as indicated by complete binding to concanavalin A-Sepharose but was larger in apparent molecular weight than a standard hTSH preparation on gel chromatography suggesting an altered glycosylation pattern. However, it was immunologically and biologically indistinguishable from two pituitary hTSH standards in an immunoradiometric and in vitro iodide trapping assay, respectively.

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*File 357: Effective October 1, DialUnit rates adjusted for unrounding.
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Set	Items	Description
S1	84703	PY=1993:1999
S2	504	AAV OR ADENO(W)ASSOCIATED
S3	504	S2 OR ADENOASSOCIATED
S4	44778	SPECIFIC?
S5	140	S3 AND S4
S6	5	S5 NOT S1
S7	17783	PROMOTER OR PROMOTERS
S8	16	S3 AND S7 NOT S1
S9	16	S8 NOT S6
S10	0	EXPRESSION(1A)CONTROL?
S11	2028	EXPRESS?(2N)CONTROL?
S12	0	S11 AND S2 NOT (S1 OR S6 OR S9)
	?	ts6/7/1 2 3 5

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DIALOG(R)File 357:Derwent Biotechnology Abs

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0144085 DBA Accession No.: 93-02137

Status of ribozyme and antisense-based developmental approaches for anti-HIV-1 therapy - adeno-associated virus vector for antisense DNA and antisense RNA expression for HIV virus-1 gene therapy (conference paper)

AUTHOR: Zaia J A; Chatterjee S; Wong K K; Elkins D; Taylor N R; Rossi JJ

CORPORATE SOURCE: Division of Pediatrics, City of Hope National Medical Center, Duarte, California 91010-0269, USA.

JOURNAL: Ann.N.Y.Acad.Sci. (660, 95-106) 1992

CODEN: ANYAA9

LANGUAGE: English

ABSTRACT: The adeno-associated virus (AAV) may be a candidate vector for use in viricide gene therapy. Antisense DNA and RNA have been shown to inhibit HIV virus-1 as either synthetic DNA or expressed RNA (intracellular immunization). Systems are being developed for inserting into the host cell genome the DNA sequences that could potentially confer resistance to HIV virus replication. A modified vector system based on the nonpathogenic, replication-defective parvo virus AAV. AAV directs the stable integration of foreign DNA encoding an HIV virus-1-specific antisense RNA. The target for the antisense RNA-transcript is the TAR sequence (a cis-acting RNA stem-loop structure in the HIV virus-1 long terminal repeat). The targeted region, TAR, is highly conserved between HIV virus-1 and SIV virus. Antisense-expressing clonal cell lines were tested for their ability to restrict both HIV virus-1 and SIV replication. Both HIV virus-1 and SIV production were inhibited in the antisense clones, SIV to a lesser degree than HIV virus-1. There was 85% inhibition of SIV replication in clone IIIC4 and 92% inhibition of HIV on day 3 posttransfection. (69 ref)

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6/7/2 DIALOG(R)File 357:Derwent Biotechnology Abs

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0138156 DBA Accession No.: 92-10648

Development of recombinant adeno-associated viruses that harbor human beta-globin cDNA/gene towards gene therapy of hemoglobinopathies - adeno-associated virus vector plasmid pAV-delta-KhbG construction and expression in 293, KB and K562 cell culture (conference abstract)

AUTHOR: Ohi S; Webb M S; Sitaric S

CORPORATE SOURCE: Department of Biochemistry, Meharry Medical College, Nashville, TN 37208, USA.

JOURNAL: Miami Short Rep. (1, 116) 1991

CODEN: 99999Y

LANGUAGE: English

ABSTRACT: Recombinant adeno-associated virus-2 (AAV2) vectors harboring human beta-globin (hbG) cDNA were constructed. Chimeric plasmid pAVhbG-psi-1 was constructed as previously described. Plasmid pAV-delta-KhbG was constructed by inserting a full-length hbG cDNA into pAV2-delta-K. The recombinant virus was produced by transfecting the chimeric plasmid into 293 cells together with plasmid pAV2 and AAV2, and preparing the cell lysate at 48 hr post-infection. Upon transfection into 293 cells, the recombinant AAV2 DNA harboring hbG cDNA was rescued from the plasmid and replicated in the cells. This in turn resulted in the production of infectious recombinant AAV. A VhbG-psi-1 expressed mRNA in the virus-infected 293, KB and K562 cells. The second recombinant virus, A V-delta-KhbG expressed hbG protein in the infected 293 cells. To make the expression of hbG cDNA/gene specific to erythroid cells, the erythroid-specific 5'-enhancer elements, DCR/LAR, were spliced into the genome of the recombinant virus. (3 ref)

6/7/3

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0134768 DBA Accession No.: 92-07260

Gene transfer in human lymphocytes using a vector based on adeno-associated virus - B-lymphocyte, T-lymphocyte transformation using AAV/neo vector, which may be useful in gene therapy

AUTHOR: Muro-Cacho C A; Samulski R J; +Kaplan D

CORPORATE SOURCE: Institute of Pathology, Case Western Reserve University, 2085 Adelbert Road, Cleveland, OH 44106, USA.

JOURNAL: J.Immunother. (11, 4, 231-37) 1992

CODEN: 5592H

LANGUAGE: English

ABSTRACT: The inverted terminal repeats of adeno-associated virus (AAV), which mediate integration at a specific site in human chromosome-19, were used to establish a vector for gene transfer into human

lymphocytes. Epstein-Barr virus-transformed B-lymphocyte JY cells were infected with vector AAV/neo containing the neomycin-resistance gene and AAV inverted terminal repeats in place of the AAV coding region. A neomycin-resistant cell was isolated after 4 wk in the presence of G418. Non-transformed T-lymphocyte CAN.1 was infected with AAV/neo during cloning. While uninfected CAJ0-10 cells (control) showed a marked reduction in proliferative activity in the presence of G418, transformed CAN.1 was not affected. There were no detectable alterations in the functional properties of CAN.1. Rescue and replication of wild-type AAV occurred with AAV super-infection. However, the vector was not rescued and did not replicate, indicating the stability of the integrated vector and demonstrating an additional level of safety incorporated in its construction. An AAV vector may be a viable alternative to retro viruses for gene therapy in lymphocytes. (32 ref)

6/7/5

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0086365 DBA Accession No.: 89-04356 PATENT

Stable and viable recombinant animal cell virus vector construction - by contacting Cre with a virus vector containing a lox site and circular DNA containing a lox site

PATENT ASSIGNEE: Du-Pont 1989

PATENT NUMBER: EP 300422 PATENT DATE: 890125 WPI ACCESSION NO.:

89-025608

(8904)

PRIORITY APPLIC. NO.: US 77145 APPLIC. DATE: 870721

NATIONAL APPLIC. NO.: EP 88111596 APPLIC. DATE: 880719

LANGUAGE: English

ABSTRACT: A method for preparing a stable and viable recombinant virus vector for animal cells by site-specific insertion of a DNA fragment into a virus vector comprises: (1) contacting Cre with a 1st lox site, which has been introduced into the DNA of the animal cell virus vector, and (2) contacting Cre with a 2nd lox site in a separate DNA molecule, which is circular so that Cre effects recombination of the circular DNA with the virus vector DNA at the 1st lox site. The initial virus vector preferably contains a selectable marker gene. The DNA fragment preferably lacks the selectable marker. The 1st lox site is introduced into a nonessential region of the vector, e.g. the gIII gene of pseudorabies virus. The DNA fragment preferably encodes a structural protein, an enzyme, a regulatory molecule, or a fragment of any of these. Each of the lox sites is preferably a loxP or a loxC2 site and the vector is preferably SV40, pseudorabies virus, polyoma virus, an adeno virus, an adeno-associated virus, herpes virus, vaccinia virus, cattle papilloma virus, Epstein-Barr virus, a baculo virus or a retro virus, especially RPV42. (19pp)

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Set Items Description
 S1 84703 PY=1993:1999
 S2 504 AAV OR ADENO(W)ASSOCIATED
 S3 504 S2 OR ADENOASSOCIATED
 S4 44778 SPECIFIC?
 S5 140 S3 AND S4
 S6 5 S5 NOT S1
 S7 17783 PROMOTER OR PROMOTERS
 S8 16 S3 AND S7 NOT S1
 S9 16 S8 NOT S6
 S10 0 EXPRESSION?(1A)CONTROL?
 S11 2028 EXPRESS?(2N)CONTROL?
 S12 0 S11 AND S2 NOT (S1 OR S6 OR S9)
 ?ts9/7/1 3-7 9 10

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0140400 DBA Accession No.: 92-12892 PATENT
 New adeno-associated virus-2 hybrid gene vector - for foreign gene
 integration and DNA rescue in mammal cell culture using a helper virus,
 e.g. plasmid ins 96/lambda-M

PATENT ASSIGNEE: Univ.Florida-Res.Found. 1992
 PATENT NUMBER: US 5139941 PATENT DATE: 920818 WPI ACCESION NO.:
 92-299352 (9236)

PRIORITY APPLIC. NO.: US 785224 APPLIC. DATE: 911025
 NATIONAL APPLIC. NO.: US 785224 APPLIC. DATE: 911025
 LANGUAGE: English

ABSTRACT: A new hybrid gene vector (capable of transduction of foreign DNA
 into a mammal cell in the presence of a promoter other than an
 adeno-associated virus (AAV) transcription promoter) comprises foreign
 DNA ligated into an AAV-2 genome, in place of or in addition to the
 cap, lip or rep coding sequence or an AAV sequence excluding the 1st
 and last 145 bp. The AAV genome is cloned in a prokaryotic or yeast
 plasmid or phage vector (e.g. plasmid pBR322), and may be the entire
 AAV DNA or a deletion mutant (e.g. dl52-91 or dl3-94), capable of
 replication on infection of the mammal cell when complemented in trans
 by an AAV gene. Methods of transducing foreign DNA into mammal cells by
 infection of cells with the vector, and methods of rescuing foreign DNA
 from transduced cells by infection with a helper virus (e.g. plasmid
 ins 96/lambda-M) containing genes for replication of the AAV genome or
 production of AAV, are also new. The vector may be used for reliable
 insertion of foreign DNA into mammal cells, so that the transferred
 genetic material is stable with respect to the insertion locus, and
 which is susceptible to expression and rescue. (12pp)

DIALOG(R)File 357:Dervent Biotechnology Abs

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0128750 DBA Accession No.: 92-01242

Construction and expression of a recombinant adeno-associated virus that
 harbors a human beta-globin-encoding cDNA - potential use in gene
 therapy of thalassemia or sickle cell anemia; gene cloning in KB, K562
 and 293 cell culture; vector construction

AUTHOR: Dixit M; Webb M S; Smart W C; +Ohi S

CORPORATE SOURCE: Department of Biochemistry, Meharry Medical College, 1005
 D.B. Todd Jr. Blvd., Nashville, TN 37208, USA.

JOURNAL: Gene (104, 2, 253-57) 1991

CODEN: GENED6

LANGUAGE: English

ABSTRACT: With the goal of using recombinant adeno-associated virus (AAV)
 for gene therapy of hemoglobinopathies, plasmid pAVh-beta-G-psi-1 was
 constructed previously, with a human beta-globin cDNA (HBB) gene
 downstream from the P40 promoter of AAV-2 DNA. Transfection of a 293
 cell culture with the plasmid resulted in expression of HBB at the mRNA
 level, and rescue and replication of the recombinant AAV genome. The
 replicated recombinant DNA was packaged into an intact virion by
 trans-complementation with plasmid pAV2 or defective helper plasmids
 (plasmid pAV-delta-Bam or plasmid pAVXB). The recombinant virus could
 be isolated by equilibrium cesium chloride density gradient
 centrifugation, at a density of 1.4 g/cm. The defective helpers were
 used to produce wild-type AAV-free recombinant AAV. The recombinant AAV
 was infectious, and produced chimeric mRNA containing the HBB sequence
 in virus-infected 293, KB (oral epidermoid carcinoma) and K562 (human
 erythroleukemia) cells. These results may be useful in designing
 strategies for gene therapy of thalassemia or sickle cell anemia. (29
 ref)

9/7/4

DIALOG(R)File 357:Dervent Biotechnology Abs

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0124445 DBA Accession No.: 91-12087 PATENT

New adeno-associated virus-derived eukaryotic vector - containing
 heterologous DNA for protein expression or especially down-regulation
 of target e.g. HIV virus-1 or herpes simplex virus-1 gene,
 intracellular immunization and gene therapy

PATENT ASSIGNEE: Nat.Inst.Health-Bethesda 1991

PATENT NUMBER: US 7527195 PATENT DATE: 900523

PRIORITY APPLIC. NO.: US 5227195 APPLIC. DATE: 900523
 NATIONAL APPLIC. NO.: US 527195 APPLIC. DATE: 900523
 LANGUAGE: English

ABSTRACT: Adeno-associated virus (AAV)-based eukaryotic vectors, and cells

transfected with these vectors, are new. The vectors are free of AAV coding sequences and consist of: (a) endogenous cis-active DNA for AAV DNA replication, encapsidation and host cell replication; (b) endogenous AAV polyadenylation signal; (c) a promoter; and (d) a heterologous DNA fragment, operably linked to (b) and (c) and present in the sense or antisense direction. The heterologous DNA fragment can encode a foreign protein or viral component. Specified AAV-based eukaryotic vectors (e.g. CWRSV:HSV-ASN and CWRSV:SN) confer intracellular resistance to HIV virus-1 and herpes simplex virus-1 (HSV-1) infection. The vectors can be used to down-regulate a targeted viral (HSV-1, HSV-1) or cellular (histocompatibility gene involved in graft rejection) gene of known sequence, or for protein expression. In a preferred process, the AAV-based vectors are used to produce an antisense mRNA complementary to a 5'-noncoding region of the primary HIV-1 RNA transcript including the core TAR sequence. The mRNA inhibits HIV-1 replication and infectious particle production. (69pp)

9/7/5
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0110288 DBA Accession No.: 90-12979

Construction of recombinant adeno-associated virus that harbors human beta-globin cDNA - vector construction for potential application in hemoglobinopathy gene therapy; gene cloning and expression in 293 cell culture (conference abstract)

AUTHOR: Ohi S; Dixit M; Tillery M K; Plonk S G

CORPORATE SOURCE: Department of Biochemistry, Meharry Medical College, Nashville, TN 37208, USA.

JOURNAL: J.Cell.Biochem. (Suppl.14A, D422) 1990

CODEN: JCEBDS

LANGUAGE: English

ABSTRACT: The possibility of developing human recombinant parvo virus vectors containing normal alpha-globin or beta-globin cDNA genes for gene therapy of hemoglobinopathies was investigated. The human beta-globin cDNA was excised from JW102 using S1-nuclease and ligated with adeno-associated virus-2 (AAV2) DNA in plasmid pAV2, downstream of the P40 promoter. Cloning of this construct in Escherichia coli DH5 resulted in isolation of recombinant plasmid pAVHbetaGHP11. Transfection via electroporation into human 293 cell culture resulted in expression of the beta-globin cDNA, as evidenced by biosynthesis of transcripts hybridizing to a human beta-globin cDNA probe. Addition of the 3'-end region of AAV DNA containing both a transcription termination signal and the replication origin for AAV to plasmid pAVHbetaGHP11 resulted in production of plasmid pAVHbetaGpsi1. Transfection of this construct into 293 cells permitted the recombinant AAV DNA containing the beta-globin cDNA to replicate inside the cell. This, in turn, resulted in production of the infectious recombinant

virus. (0 ref)

9/7/6
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0110266 DBA Accession No.: 90-12957

Construction and replication of an adeno-associated virus expression vector that contains human beta-globin cDNA - plasmid pAVh-beta-GHP11 and plasmid pAVh-beta-G-psi-1 construction; potential application in gene therapy of e.g. sickle cell anemia or thalassemia

AUTHOR: Ohi S; Dixit M; Tillery M K; Plonk S G

CORPORATE SOURCE: Department of Biochemistry, Meharry Medical College, 1005 D.B. Todd Jr. Blvd., Nashville, TN 37208, USA.

JOURNAL: Gene (89, 2, 279-82) 1990

CODEN: GENED6

LANGUAGE: English

ABSTRACT: With the goal of using an adeno-associated virus (AAV) as a gene transfer vector for gene therapy of hemoglobinopathies (e.g. sickle cell anemia or thalassemia), human beta-globin cDNA was ligated downstream from the P40 promoter of the AAV-2 genome. To circumvent difficulties of cloning DNA containing palindromic sequences, 2 of which exist in the termini of the AAV genome, a stepwise approach handling 1 palindrome at a time was devised to construct a chimeric expression vector, plasmid pAVh-beta-GHP11. Electroporation of the construct into a human 293 cell culture resulted in expression of the cloned human beta-globin cDNA, as evidenced by the biosynthesis of transcripts hybridizable to a human beta-globin cDNA probe. Addition of the 3'-end region of AAV DNA containing both the transcription termination signal and DNA replication origin for AAV to the construct (to give plasmid pAVh-beta-G-psi-1) permitted the recombinant AAV genome to be rescued and replicate in the cell. (17 ref)

9/7/7
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0106673 DBA Accession No.: 90-09364

Production and expression of recombinant adeno-associated viruses harboring human beta-globin cDNA - adeno-associated virus expression in 293 cell culture; potential gene therapy for hemoglobinopathy diseases (conference abstract)

AUTHOR: Ohi S; Dixit M; Plonk S G

CORPORATE SOURCE: Meharry Medical College, Nashville, TN 37208, USA.

JOURNAL: FASEB J. (4, 7, A2288) 1990

CODEN: FAJOEC

LANGUAGE: English

ABSTRACT: 2 Plasmids that harbor human beta-globin (hbG) cDNA downstream of the P40 promoter of adeno-associated virus-2 (AAV2) DNA were

constructed with the aim of using recombinant human parvo virus for hemoglobinopathy gene therapy. Plasmid pAVbetaGpsil contains a partial hbG cDNA derived from plasmid JW102, whereas plasmid pAVdeltaKhbG contains a full-length hbG cDNA derived from plasmid pB6-6. Upon transfection, pAVbetaGpsil expressed chimeric RNAs containing hbG sequences in human 293 cells. Recombinant genomes were rescued from both plasmids and replicated in the cell. This led to the production of infectious recombinant AAV. When infected in 293 cells, the virus preparation resulted in efficient expression of hbG mRNAs in the cell. (3 ref)

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0086328 DBA Accession No.: 89-04319

Construction and characterization of recombinant adeno-associated virus genome containing human beta-globin cDNA - gene cloning and expression in human cell culture; potential sickle cell anemia or thalassemia gene therapy (conference abstract)

AUTHOR: Ohi S; Dixit M; Tillery M K

CORPORATE SOURCE: Department of Biochemistry and the Sickle Cell Center, Meharry Medical College, Nashville, TN 37208, USA.

JOURNAL: J Cell Biol. (107, 6, Pt.3, 304a) 1988

CODEN: JCLBA3

LANGUAGE: English

ABSTRACT: The human parvo virus, adeno-associated virus, is a useful vector for cloning and expression of foreign genes. With the aim of construction of recombinant human parvo viruses containing either alpha-globin or beta-globin genes for gene therapy of hemoglobinopathies, such as sickle cell anemia and thalassemia, a cDNA sequence for human beta-globin was isolated and inserted downstream of the p40 promoter of adeno-associated virus. The beta-globin cDNA was excised from plasmid JW102 using S1 nuclease. The fragment was treated with Escherichia coli DNA-polymerase-I (EC-2.7.7.7), Klenow fragment and blunt-end ligated to plasmid pBR322, followed by cloning in Escherichia coli HB101. 1 Clone, plasmid pHbetaGS3, was amplified and the intact beta-globin cDNA region was excised on a HindIII-NheI fragment. The fragment was treated with Bal31 and blunt-end ligated to plasmid pAV2 downstream of the p40 promoter (HindIII site). From plasmid pAV2 a KpnI fragment was deleted (plasmid pAVdeltaKpn) to accommodate the foreign DNA. Expression of beta-globin under the control of p40 promoter was tested in human 293 cell culture and pluripotent K562 cell culture. (2 ref)

Expression and rescue of a nonselected marker from an integrated AAV vector - chloramphenicol-acetyltransferase gene cloning in human cell culture using adeno-associated virus vector

AUTHOR: Mendelson E; Smith M G; Carter B J

CORPORATE SOURCE: Laboratory of Molecular and Cellular Biology, National Institute of Diabetes, Digestive, and Kidney Diseases, Building 8, Room 304, National Institutes of Health, Bethesda, Maryland 20892, USA.

JOURNAL: Virology (166, 1, 154-65) 1988

CODEN: VIRLAX

LANGUAGE: English

ABSTRACT: Rep+ and rep- adeno-associated virus (AAV) vectors (plasmid pEM15 and plasmid pEM612 respectively) were constructed, containing a chloramphenicol-acetyltransferase (EC-2.3.1.28) (CAT) gene driven by the AAV p40 promoter, and a neo gene, driven by a herpes virus thymidine-kinase (EC-2.7.1.21) gene promoter. The vectors were transfected into a human 293 cell or HeLa cell culture, geneticin-resistant cells were selected, and cells were screened for CAT expression. With 293 cells, most rep- clones showed high CAT expression, but only 50% of rep+ clones expressed CAT, at a low level. With HeLa cells 25% of rep+ and rep- clones expressed CAT, some rep+ clones giving high yields. The rep+ vectors were also analyzed by rescue after superinfection with adeno virus and by Southern blot. AAV-CAT DNA could be rescued from 50% of HeLa cells but not from 293 cells. Non-rescue could be due to rearrangement of AAV termini or the rep gene. Western blot analysis showed low constitutive expression of rep protein in 1 293 cell clone and 2 HeLa cell clones. Thus, the AAV p40 promoter could drive expression of non-selected markers in integrated vectors, which could then be rescued. (26 ref)

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